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# Essentials of Sleep Medicine

An Approach for Clinical Pulmonology

 Humana Press

# Respiratory Medicine

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M. Safwan Badr  
Editor

# Essentials of Sleep Medicine

An Approach for Clinical Pulmonology

 Humana Press

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# Preface

Sleep has fascinated poets, lovers and philosophers since time immemorial. It was a metaphor for rest, rejuvenation and restoration. Physicians viewed sleep and thought of sleep as a “safe harbor” keeping illness away, and as a cuddly “teddy bear” giving warmth and serenity. Few physicians appreciated sleep complexity beyond the elemental aspects; patients need rest and sleep. Disorders of sleep were the subject of interesting discussions at teaching conferences but the only condition worthy of discussion was lack of sleep, and it was often due to tension or anxiety.

The image of sleep as a quiescent period changed dramatically when scientists began to uncover the mysteries of sleep: the good, the bad and the ugly! The discovery of REM sleep altered the popular image and revealed a fascinating constellation of active processes throughout the body. However, it was sleep apnea that propelled sleep into mainstream medicine. This is a condition where sleep is anything but rest. We learned that sleep can be seen as a “grizzly bear” as we discovered that sleep apnea has significant adverse consequences and may contribute to mortality and to traffic fatalities.

The initial phase of sleep medicine was marked by different specialties providing care for conditions deemed within their domain. Neurologists, psychiatrists and pulmonologists focused on different disorders and different approaches to diagnosis and treatment. Fortunately, we soon discovered that sleep is an interdisciplinary field, transcending traditional, system-based specialties. Patients present with complaints and not diagnoses, and sleep disorders share a small number of sleep-related complaints. We learned that snoring may represent a serious condition, that daytime sleepiness is not a sign of narcolepsy per se, and that insomnia is not necessarily due to anxiety or depression. Therefore, physicians who care for any sleep disorder must learn about all sleep disorders.

The focus of this book is practical; relevant facts help the busy practicing physicians provide better care for sleep disorders as part of a comprehensive care. It is entitled “for the pulmonologist” but can equally benefit internists, neurologists, psychiatrists and family physicians. Residents and fellows may find the focused description and practical approach beneficial. One specific focus is the notion that most

clinical conditions interact with sleep, many medications affect sleep and some are aggravated by sleep.

This book represents the collective effort of a team of professionals. Each chapter was written by an expert in the field blending seasoned experts with emerging leaders.

Editing a book is a challenging process as one tries to keep a group of busy and forgetful academicians on schedule. I am grateful to Amanda Quinn and Joni Fraser of Springer for their support, guidance, and superb organizational skills. I would like to thank Springer Science and Business Media for supporting this project.

Detroit, MI

M. Safwan Badr

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# Chapter 1

## Normal Sleep

James A. Rowley and M. Safwan Badr

**Keywords** NREM sleep • REM sleep • EEG • Upper airway resistance • Hypocapnic apneic threshold • Critical closing pressure ( $P_{crit}$ ) • Heart rate variability • Esophageal sphincter

### Normal Sleep Stages and Architecture

Normal human sleep is generally divided into four stages. Consensus definitions for the visual scoring of sleep were published in 2007 and the reader is referred to the American Academy of Sleep Medicine Scoring Manual for full definitions and criteria for the scoring of sleep on polysomnograms [1, 2]. The following will provide a brief overview of the electroencephalographic (EEG) characteristics of the different sleep stages (Fig. 1.1).

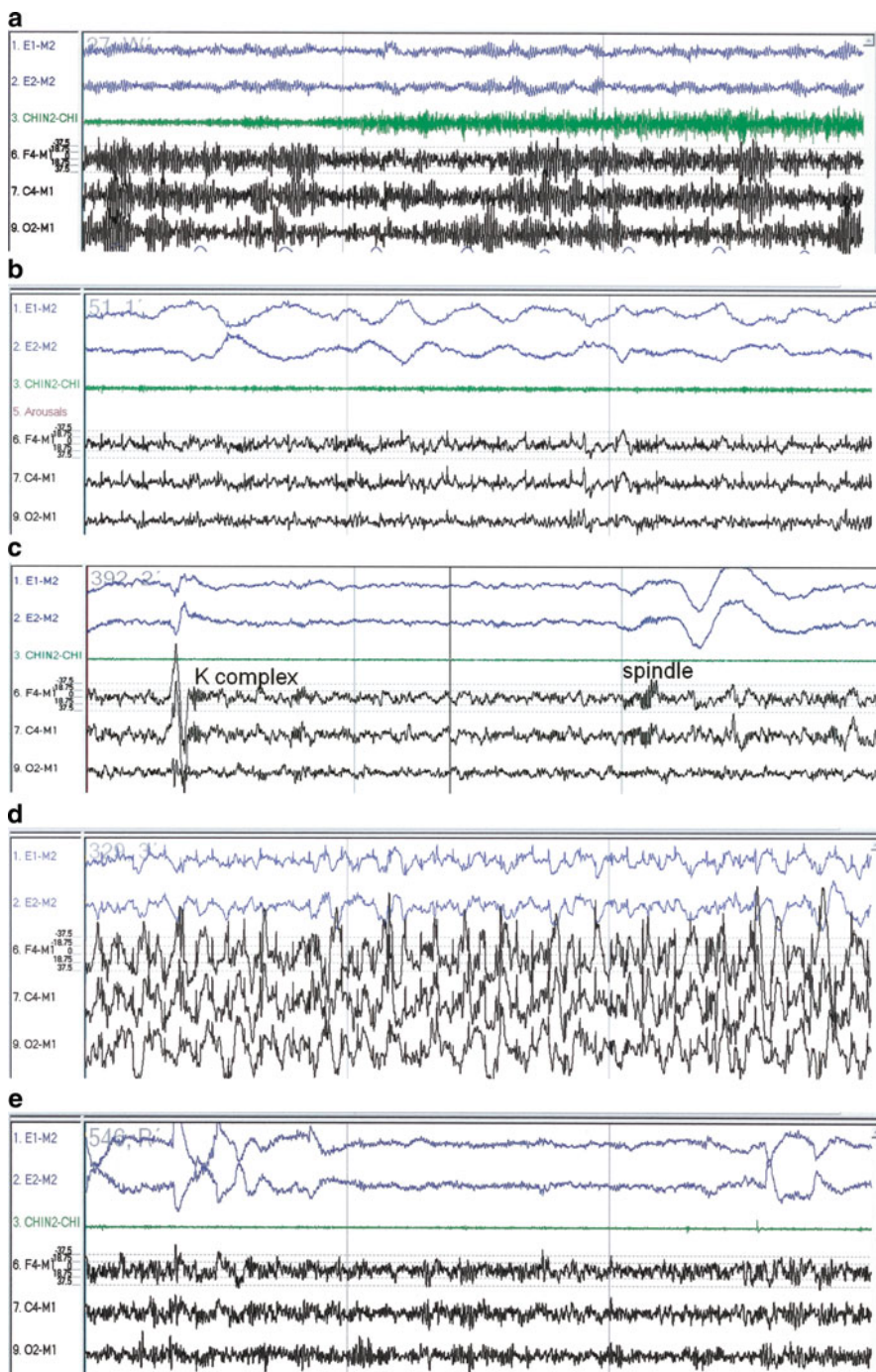
Full wakefulness is characterized by mixed-frequency, low amplitude EEG activity, often in association with high chin muscle tone, eye blinks, and rapid eye movements. As the patient transitions to sleep with eyes closed, wakefulness is characterized by a 8–13-Hz sinusoidal activity called alpha sleep. Alpha sleep is best recorded over the occipital region and is attenuated by eye opening.

Nonrapid eye movement (NREM) sleep composes the majority of the night and is characterized by the predominance of homeostatic mechanisms for breathing, cardiovascular and gastrointestinal function, and normal thermoregulation. NREM sleep is divided into three stages. N1 sleep is a transitional period during which the individual still usually has some awareness of his/her environment. N1 sleep is characterized by a slowing of the background wake EEG frequencies with a

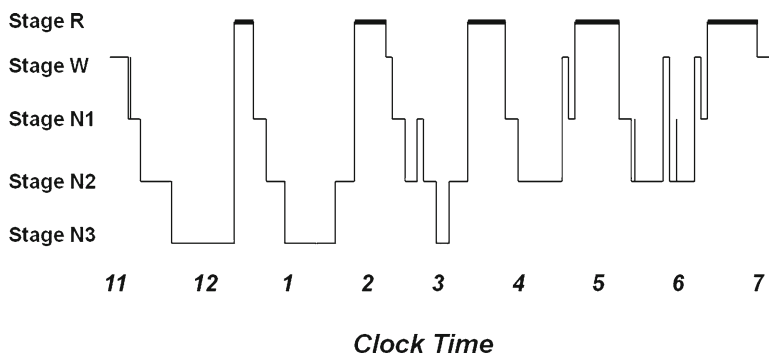
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**Fig. 1.1** Representative 30-s epochs of sleep stages. **(a)** Wakefulness with alpha rhythm; **(b)** stage N1; **(c)** stage N2 with K-complex and spindle; **(d)** stage N3 (slow wave sleep); and **(e)** stage R. For all epochs: E1-M2: left electro-oculogram; E2-M2: right electro-oculogram; chin 2: chin EMG; F4-M1: right frontal EEG; C4-M1: right central EEG; O2-M1: right occipital EEG



**Fig. 1.2** Representative hypnogram showing normal sleep architecture

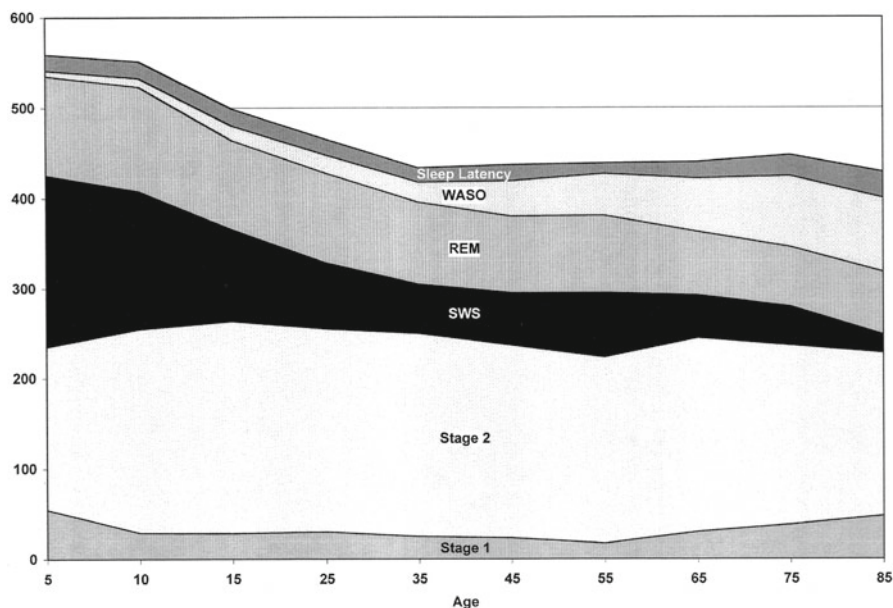
predominance of low amplitude activity in 4–7 Hz (often referred to as theta activity). Slow eye movements are commonly observed during N1 sleep. N2 sleep, at which time the individual generally is no longer aware of his/her environment, is characterized by the appearance of sleep spindles and K complexes superimposed on a background of theta activity. Sleep spindles are rhythmic sinusoidal waves of 12–14 Hz, usually best recorded on central EEG leads. K complexes are diphasic waves having a well-delineated sharp negative component followed by a slow positive component. N3 sleep, commonly known as slow wave sleep, is scored when slow wave activity is recorded on >20% of an epoch. By definition, slow waves are of low frequency (generally 0.5–2 Hz) and have large amplitude (>75  $\mu$ V).

As opposed to NREM sleep, rapid eye movement (REM or Stage R) is characterized by variations and instability in cardiopulmonary function and instability of body temperature control. In addition, Stage R is characterized by dreaming, relative atonia of all muscle groups except the diaphragm and in men, erections. On EEG, Stage R is characterized by a low amplitude, mixed frequency EEG, similar to that seen in Stage N1 sleep. In addition, Stage R is characterized by the presence of REMs and decreased chin muscle tone. Stage R is a unique time of the night in that dreaming occurs during Stage R sleep.

Sleep architecture describes the organization of the sleep stages over the course of the night (Fig. 1.2). The normal sleep cycle in a young adult (generally considered the standard) begins with transitioning from wakefulness to N1 sleep and then quickly transitioning to N2 and N3 sleep. The first occurrence of Stage R sleep is generally at about 90 min and individuals then cycle between NREM and REM sleep every 90–110 min throughout the night. In general, N3 sleep predominates in the first half of the night whereas Stage R predominates in the second half of the night. For an average individual in their second decade, Stage N1 is 2–5% of the total sleep time, Stage N2 is 45–55%, Stage N3 13–23%, and Stage R is 20–25% [3].

Overall sleep architecture is dependent upon stage of development and aging (Fig. 1.3). For instance, infants generally spend up to 50% of the night in Stage R sleep and often have a cycle of REM sleep prior to NREM sleep. In addition, the





**Fig. 1.3** Changes in sleep stages as a percentage of sleep time across the age span. *WASO* wake after sleep onset; *REM* rapid eye movement sleep; *SWS* slow wave sleep. See text for details (reprinted by permission from Ohayon et al. [3])

duration of the NREM–REM cycle is 60 min through most of childhood. Over the span of time between young adulthood to elderly, there are changes in most sleep stages, including decreased total sleep time and sleep efficiency, increased percentage of Stages N1 and N2, decreased percentage of Stages N3 and R. These changes with aging have been shown to be more prominent in men than women [3, 4].

## Breathing During Sleep: Ventilation and the Upper Airway

### *Summary of Normal Breathing and Ventilation During Sleep*

Ventilatory motor output during sleep decreases from its normal levels in wakefulness, leading to decreased tidal volume and minute ventilation. The decreased ventilation is accompanied by reduced upper-airway dilator muscle activity resulting in decreased upper-airways caliber and increased airflow resistance. These biological changes may account for the observed increase in  $\text{PaCO}_2$  and decrease in  $\text{PaO}_2$  during sleep, despite the diminished overall metabolic rate. A decrease in chemoresponsiveness during sleep may also explain the increased  $\text{PaCO}_2$ . Overall, breathing becomes more dependent on chemical stimuli, especially  $\text{PaCO}_2$ .

In contrast to NREM sleep, REM sleep is characterized by variability in ventilation. This variability consists of sudden changes in respiratory amplitude and frequency associated with the periods of phasic REMs. Because of this variability, minute ventilation in REM sleep has been shown to be the same, increased, or decreased compared with NREM sleep. Upper-airway resistance has also been reported variably as either the same or increased compared to wakefulness and NREM sleep. Finally, hypercapnic and hypoxic ventilatory chemoresponsiveness is decreased in REM sleep compared to wakefulness and possibly even NREM sleep.

### ***Effect of Sleep on Control of Breathing***

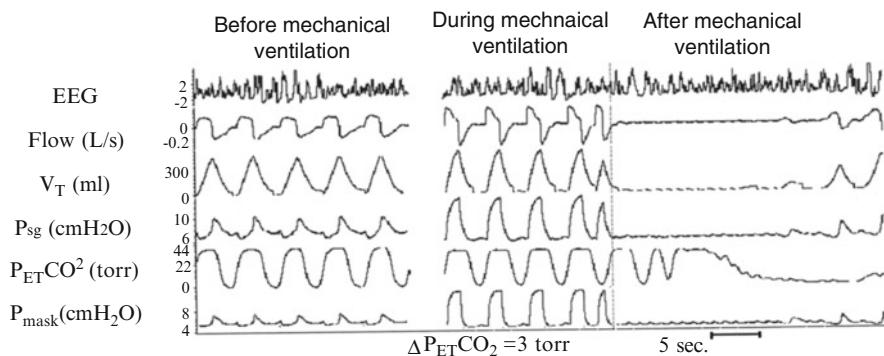
Chemoresponsiveness refers to changing ventilation in response to changes in chemical stimuli. Chemosensitivity is influenced by changes in neural activity during sleep. Thus, hypoxic and hypercapnic chemoresponsiveness contributes to maintaining ventilation during sleep. Conversely, hypocapnia is a potent inhibitor of ventilation during NREM sleep and is a key mechanism of central apnea [5].

The sleep state is characterized by decreased ventilatory response to hypercapnia (HCVR) in human adults compared to wakefulness [6–12]. While the sensitivity to  $\text{PaCO}_2$  does not appear to differ within NREM sleep stages, the HCVR during REM stage is depressed further compared with NREM sleep [6, 8]. Similarly, hypoxic ventilatory responsiveness (HVR) is also diminished during NREM sleep compared to wakefulness, with a further decrease in REM sleep [10, 13–15]. Nevertheless, the effect of sleep on chemoresponsiveness is confounded by the sleep effect on upper airway mechanics and associated decrease in ventilation.

The loss of wakefulness stimulus to breathe renders ventilation during NREM sleep critically dependent on chemoreceptor stimuli ( $\text{PaO}_2$  and  $\text{PaCO}_2$ ). Reduced  $\text{PaCO}_2$  is a powerful inhibitory factor of ventilation during sleep. Therefore, central apnea develops when  $\text{PaCO}_2$  is reduced below a highly reproducible hypocapnic apneic threshold, unmasked by NREM sleep [5] (Fig. 1.4). Hypocapnia is probably the most important inhibitory factor during NREM sleep. Hypocapnia, secondary to hyperventilation, is key to the genesis of central sleep apnea in congestive heart failure [16], and idiopathic central sleep apnea [17, 18], and may be relevant to the pathogenesis of obstructive sleep apnea (OSA) as well [19–21].

### ***Effect of Sleep on Upper-Airway Structure and Function***

The sleep state is a challenge, rather than a rest period, for the ventilatory system. Consequences of loss of wakefulness include reduced activity of upper-airway dilators, reduced upper-airway caliber, increased upper-airway resistance, loss of load compensation, and increased pharyngeal compliance and collapsibility. Ultimately, these changes lead to reduced tidal volume and hypoventilation.



**Fig. 1.4** Induced hypocapnic central apnea during NREM sleep. Nasal mechanical ventilation was used to decrease end-tidal  $\text{PCO}_2$  ( $P_{\text{ETCO}_2}$ ). Cessation of mechanical ventilation caused central apnea.  $P_{\text{sg}}$  supraglottic pressure;  $P_{\text{mask}}$  mask pressure

The musculature of the upper airway consists of 24 pairs of striated muscles extending from the nares to the larynx [22, 23]. There are at least ten muscles that are classified as pharyngeal dilators. There are two patterns of electrical discharge from these muscles: tonic (constant) activity, independent of phase of respiration, and phasic activity, occurring during one part of the respiratory cycle. It is widely accepted that upper-airway narrowing during sleep is due to a sleep-related decrease in upper-airway muscle activity. During NREM sleep, available evidence indicates a reduction in either the tonic or phasic activity for a variety of upper-airway muscles [23], including the levator palatini [24], tensor palatini [25], palatoglossus [24], and geniohyoid [26]. The effect of REM sleep on upper-airway muscle activity is more compelling, with strong evidence that activity of phasic upper-airway dilating muscles, such as the genioglossus, is greatly attenuated during REM sleep [27, 28], particularly during periods of phasic REMs [29, 30].

The response of upper-airway muscle to chemical and mechanical perturbations may be more relevant physiologically than reduced baseline activity. Pharyngeal muscles display an attenuated response to negative pressure during NREM [31–33] and REM sleep [34] compared to wakefulness. Similarly, responsiveness of the genioglossus muscle to hypercapnia is also attenuated during sleep [35]. Decreased responsiveness to challenges indicates that upper-airway muscles are less able to maintain upper-airway patency in the face of chemical or mechanical perturbations.

The evidence for increased upper-airway resistance during sleep is compelling, even in normal subjects [36–40]. The preponderance of evidence is that there are no further increases in upper-airway resistance as subjects transition from NREM to REM sleep [39–41]. However, it is important to note that upper-airway resistance provides only a partial picture of the dynamic behavior of the pharyngeal airway during sleep. Specifically, upper-airway resistance is generally expressed as a single number representing the slope of pressure–flow relationship during inspiration. This computation is predicated on a constant relationship between driving pressure and inspiratory flow, which is true during normal breathing in normal subjects. However,

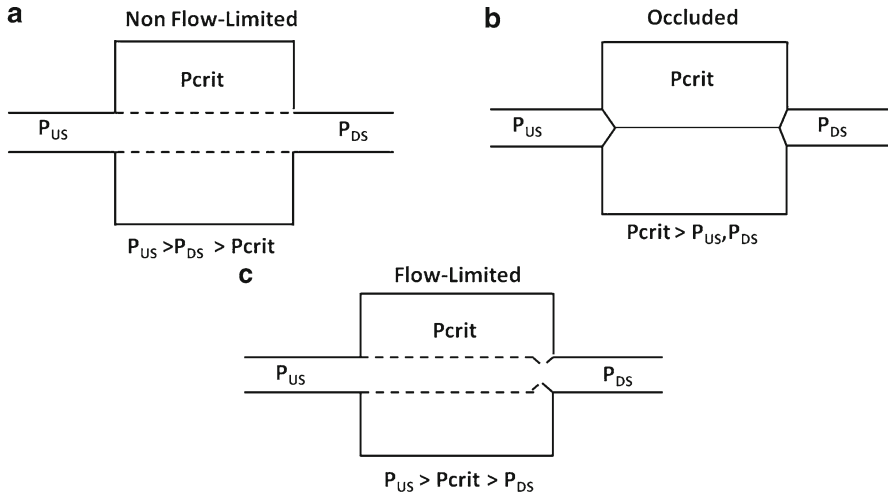
many subjects exhibit inspiratory-flow limitation, in which the pressure–flow graph demonstrates a changing relationship culminating in complete dissociation between pressure and flow (pressure continues to decrease with no further increase in flow). While many authors equate increased upper airway resistance to increased collapsibility, it is in reality a rather limited surrogate for susceptibility to pharyngeal closure during sleep [42].

Using nasopharyngoscopy during naturally occurring sleep in normal subjects, Rowley et al. have shown that pharyngeal cross-sectional area is decreased during sleep at both the retropalatal and retroglossal levels [39, 40]. During NREM sleep, both retropalatal cross-sectional area and retroglossal cross-sectional area decreased to ~70% of the awake baseline cross-sectional area. The decreased cross-sectional area is consistent with a decrease in upper-airway dilator activity with the onset of NREM sleep. In REM sleep, retropalatal cross-sectional area did not decrease further compared to NREM sleep [40]. In contrast, retroglossal cross-sectional area did decrease further during REM compared to NREM sleep [39].

The ability of the ventilatory control system to compensate for changes in resistance is essential for the preservation of alveolar ventilation. Increased resistance is an example of resistive load, leading, during wakefulness, to increased effort to maintain ventilation and  $\text{PaCO}_2$ . In contrast, hypoventilation occurs immediately upon imposing a resistive load during NREM sleep, perhaps implying that loads are not perceived during sleep [43]. Therefore, resistive loading results in decreased tidal volume and minute ventilation and, hence, alveolar hypoventilation. The ensuing elevation of arterial  $\text{PaCO}_2$  restores ventilation toward normal levels. Teleologically, failure to respond to loads preserves sleep continuity. The cost of allowing sleep continuity is a mild elevation of  $\text{PaCO}_2$ . In fact, elevated  $\text{PaCO}_2$  during sleep is one of few physiologic situations where hypercapnia is tolerated.

The walls of the pharyngeal airway consist of compliant soft tissue structures, amenable to changes in pressure during the respiratory cycle. During wakefulness, upper-airway caliber is constant during inspiration, with a decreased caliber during expiration, returning to inspiratory values at end-expiration. This finding has been observed in both normal subjects [44, 45] and patients with sleep apnea [45] using either computerized tomographic (CT) scanning or nasopharyngoscopy. Using nasopharyngoscopy, NREM sleep was associated with significant dynamic within-breath changes in cross-sectional area, reaching a nadir at midinspiration [45], with a rapid increase in cross-sectional area during expiration [20].

The dynamic changes in upper-airway patency during sleep can be best investigated using compliance as a measurement. Traditionally, compliance is the change in volume for a given change in pressure. Compliance of the pharyngeal wall is an important modulator of the effect of pressure changes on upper-airway patency. Traditionally, upper-airway compliance has been measured in a static fashion by measuring changes in cross-sectional area at different levels of pressure applied to the upper airway [46–48]. Use of this technique has demonstrated that compliance is increased as the pharyngeal caliber decreases [46, 47, 49]. In contrast, we have combined measurement of cross-sectional area via fiberoptic nasopharyngoscopy and measurement of intraluminal pressure at the same level during NREM and



**Fig. 1.5** Starling resistor model of the upper airway. In a starling resistor there is a collapsible segment surrounded by an upstream and downstream noncollapsible segments. In this model,  $P_{crit}$  is assumed to be equal to the pressure surrounding airway.  $P_{US}$  upstream (nasopharyngeal) pressure;  $P_{DS}$  downstream (hypopharyngeal) pressure. In (a), both the  $P_{US}$  and  $P_{DS}$  are greater than  $P_{crit}$ , the airway is wide open and flow will be proportional to the difference between  $P_{US}$  and  $P_{DS}$ . In (b), the  $P_{crit}$  is greater than both  $P_{US}$  and  $P_{DS}$ , the airway is closed, and there is no flow. In (c),  $P_{US}$  is greater than  $P_{crit}$  but  $P_{crit}$  is greater than  $P_{DS}$ , creating a condition of flow limitation; flow is proportional to the difference between  $P_{US}$  and  $P_{crit}$ .

REM sleep. These studies have confirmed that retropalatal compliance is increased during NREM sleep compared to wakefulness; in contrast, retropalatal compliance during REM sleep is similar to that in wakefulness [40]. At the retroglottal level, however, compliance was not increased during either NREM or REM sleep compared to wakefulness [39]. Thus, pharyngeal compliance was not increased, despite the known absence of upper-airway muscle activity during REM sleep.

Collapsibility refers to the propensity of the upper airway to collapse or obstruct under certain conditions. While often used interchangeably with compliance, it differs from compliance in that compliance measures the changes in upper-airway area for given changes in pressure and not the propensity to collapse. Upper-airway collapsibility has been primarily measured using the critical closing pressure or  $P_{crit}$ .

Measurement of critical closing pressure or  $P_{crit}$  is based upon the concept of the Starling resistor (Fig. 1.5) [50]. In a Starling resistor, maximal flow through the resistor is dependent upon the resistance of the segment upstream and the pressure surrounding the collapsible segment. In normal subjects, the application of progressively negative nasal pressure (upstream pressure) results in inspiratory-flow limitation, followed by complete upper-airway obstruction [51]. Thus, this model of upper-airway mechanics has several advantages as a method to study upper-airway collapsibility. First, it most closely approximates the inspiratory-flow limitation that characterizes the breathing of many subjects with snoring. Second, the model allows a functional approach to the upper airway, which is key, given the complicated anatomy of the upper airway.

Applying this model to humans, it has been shown that across the spectrum of sleep-disordered breathing, active  $P_{\text{crit}}$  becomes progressively more positive, indicative of increased propensity for airway collapse [51–53]. For instance,  $P_{\text{crit}}$  in normal subjects is generally  $<10 \text{ cmH}_2\text{O}$  while in patients with predominant hypopneas it is between 0 and  $-5 \text{ cmH}_2\text{O}$  and in patients with predominant apneas it is  $>0 \text{ cmH}_2\text{O}$ . Kirkness et al. found that in a group of 166 men and women with and without sleep disordered breathing, passive  $P_{\text{crit}}$  is higher in men and increases with increasing age and BMI [54]. In addition, in these studies sleep apnea was largely absent in subjects with a passive or active  $P_{\text{crit}}$  more negative than  $-5 \text{ cmH}_2\text{O}$  [54, 55].

## Cardiovascular Function During Sleep

NREM sleep is characterized by autonomic stability, driven by increased vagal nerve activity and parasympathetic tone when compared to wakefulness. The increased vagal activity results in an overall decrease in heart rate during NREM sleep and frequent sinus arrhythmia coupled to respiratory variation. In sinus arrhythmia, there is an increase in heart rate during inspiration to accommodate increased venous return with a decrease in heart rate during expiration. Because of the increased vagal tone, NREM sleep is associated with an increase in heart rate variability compared to wakefulness [56, 57]. In addition, NREM sleep is associated with a decrease in cardiac output and a decrease in blood pressure [58, 59]. Loss of the usual nocturnal decrease in blood pressure is frequently seen in patients with OSA [60, 61]. Finally, NREM sleep is associated with decrements in both global cerebral blood flow and metabolism, both of which are particularly decreased during slow wave sleep [62–64].

In contrast, during REM sleep, heart rate becomes increasingly variable with transient increases in heart rate in association with the REMs. These transient increases in heart rate are not observed following interruption of sympathetic neural output to the heart in animals, suggesting that the surges in heart rate are sympathetically driven [65]. In addition, heart rate variability is increased in REM sleep compared to NREM sleep [57, 66]. In association with the transient increases in heart rate, there are also transient increases in blood pressure. In addition, in animal models, the transient increases in heart rate are associated with profound increases in coronary blood flow [65]. In animal model of coronary stenosis, coronary blood flow is decreased despite the increased heart rate [67], suggesting that the myocardium is at increased risk of ischemia during REM sleep. However, human studies have not been performed to confirm this finding. Finally, in contrast to NREM sleep, global cerebral blood flow and metabolism are unchanged compared to wakefulness in REM sleep [63]. However, there is evidence that there are significant regional differences in cerebral blood flow during REM sleep, with increased blood flow to areas of the brain associated with the generation of REM sleep such as the brainstem and thalamus with continued decreased blood flow to other areas such as the prefrontal and frontoparietal cortices [62, 68].

## Endocrine Function During Sleep

The levels of circulating endocrine hormones are generally influenced either by circadian rhythms or the sleep–wake cycle [69, 70]. Growth hormone and prolactin are examples of hormones whose circulating levels are related to the sleep–wake cycle. Growth hormone secretion is tightly related to the sleep–wake cycle; when the sleep period is shifted, the major growth hormone pulse is also shifted and the growth hormone secretion is absent in sleep deprivation. Maximal growth hormone secretion is during slow wave sleep, though this pattern is more generally observed in men than women and is less pronounced with aging. While prolactin levels generally increase in the afternoon after the usual nadir at noon, there is a major elevation in prolactin levels shortly after sleep onset. In addition, during naps, there is generally a pulse of prolactin activity irrespective of the time of day.

Adrenocorticotrophic hormone and cortisol follow a circadian pattern. Levels of these hormones are generally increased in the later part of the night and are maximal in the early morning; levels then decline through the day with minimal levels generally around midnight.

Circulating levels of thyroid-stimulating hormone (TSH) are influenced by both circadian rhythms and the sleep–wake cycle. TSH levels are low during the day and increase in the evening under circadian influences. With sleep onset, levels decrease with the inhibitory influence primarily noted during slow wave sleep. Consistent with the sleep–wake cycle influence, TSH levels continue to increase during sleep deprivation.

## Gastrointestinal Function During Sleep

The effects of sleep on the gastrointestinal system are driven by a variety of processes, including increased parasympathetic activity and circadian rhythms [71]. An example of decreased parasympathetic activity is the observed decrease in salivation during sleep. In contrast, basal gastric acid secretion follows a circadian rhythm, with peak secretion between 10 pm and 2 am and relative absence of basal secretion in the absence of meal stimulation [72].

Sleep also affects the mobility of the gastrointestinal tract. The frequency of swallowing decreases significantly during sleep while there is also evidence of decreased esophageal peristaltic waves during NREM sleep [71, 73]. Traditionally, it has been believed that upper esophageal sphincter tone is unchanged during sleep while lower esophageal sphincter tone is decreased. However, recent data indicates that upper sphincter tone is more vulnerable to decreased tone during sleep with a smaller change in the lower esophageal sphincter tone, which generally stays greater than intragastric pressure [73–75]. Finally, there is evidence that the phasic myoelectrical activity and motor function of the stomach and intestines is decreased



during sleep, with some evidence that the decrease could be in part circadian in origin [71, 73, 76, 77].

One of the major effects of the changes in gastrointestinal function during sleep is increased acid contact time [78]. Generally, during wakefulness, gastroesophageal reflux is a postprandial event and acid is rapidly cleared from the esophagus because of increased salivary gland secretion, increased swallowing, and primary peristalsis. While GER events are less frequent during sleep, events are associated with decreased acid clearance and increased acid contact time because of the sleep-related decreases in salivation, swallowing, and peristalsis. In addition, heartburn is a waking conscious phenomenon and this sensation is generally absent during sleep. Increased acid contact time has been shown to be related to proximal migration of refluxed gastric contents [79] and is a potential mechanism for the development of esophagitis, chronic cough, and exacerbations of bronchial asthma [71].

## Summary of Keypoints

- Normal sleep is generally divided into four stages of sleep: N1, N2, N3 (all stages of NREM sleep), and R (REM sleep). The stages of sleep are distinguished by specific EEG and EOG characteristics.
- NREM sleep is characterized by the predominance of homeostatic mechanisms for breathing, cardiovascular and gastrointestinal function, and thermoregulation.
- REM sleep is characterized by dreaming, inhibition of muscle activity, and instability of cardiopulmonary systems.
- In humans, sleep cycles between NREM and REM every 90–110 min with slow wave sleep (N3) predominant in the first half of the night and REM sleep predominant in the second half of the night.
- NREM sleep is associated with decreased tidal volume, stable respiratory rate, decreased chemoresponsiveness to  $\text{CO}_2$  and  $\text{O}_2$ , and increased  $\text{PCO}_2$  compared to wakefulness. There is also autonomic stability with a vagal predominance, resulting in bradycardia and frequent arrhythmia.
- While REM sleep is also associated with decreased chemoresponsiveness, there is greater variability in respiration, heart rate, and regional blood, generally in association with the REMs.
- Sleep is associated with changes in upper-airway structure and function including decreased cross-sectional area, and increased resistance, compliance, and collapsibility.
- Growth hormone and prolactin are tightly associated with the sleep cycle showing increase during sleep. Adrenocorticotrophic hormone and cortisol demonstrate a circadian rhythm with maximal levels in the early morning.
- Sleep is associated with decreased salivation, increased gastric acid secretion, decreased swallowing and esophageal peristalsis, and overall decreased myoelectrical activity of the gastrointestinal tract.



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# Chapter 2

## Pharmacology of Sleep

Susmita Chowdhuri

**Keywords** GABA  $\gamma$ (gamma)-amino butyric acid • Hypocretin antagonist • Benzodiazepines • Nonbenzodiazepine receptor agonists • Melatonin receptor agonist • Serotonin and norepinephrine reuptake inhibitors • Antidepressants • Amphetamines • Modafinil • Sodium oxybate

### Introduction

Drugs that modulate sleep and wakefulness operate by modifying the activity of key sleep–wake neurotransmitters in the brain. Wakefulness-promoting nuclei include the orexinergic lateral hypothalamus, the histaminergic tuberomammillary nucleus, the cholinergic pedunculopontine (PPT) and laterodorsal (LDT) tegmental nuclei, the noradrenergic locus coeruleus, the serotonergic raphe nuclei, and the dopaminergic ventral tegmental area (Table 2.1). The major sleep-promoting nucleus is the GABAergic ventrolateral preoptic (VLPO) nucleus of the hypothalamus that sends projections to the brainstem and hypothalamic wake promoting neurons in the locus coeruleus, raphe nucleus, and tuberomammillary nucleus and these in turn send projections to the VLPO. Reciprocal inhibition of these neurons promotes sleep and wakefulness [1]. In addition, the hypocretin/orexin neurons in the lateral thalamus reinforce and stabilize the wake promoting area [1]. Glutamate is also wake promoting.

Sedatives and stimulants modulate the activity of these sleep and wake promoting nuclei. Overall, drugs that are *agonistic* to the sleep-promoting GABA receptor or that are *antagonistic* to the wake-promoting neurotransmitters, norepinephrine, serotonin, histamine, and acetylcholine, are sedating [2]. Conversely, drugs that activate

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**Table 2.1** Neurotransmitters and sleep

Sleep promoting neurotransmitters/neurohormone	Wake promoting neurotransmitters
GABA	Norepinephrine
Adenosine	Dopamine
Melatonin <sup>a</sup>	Serotonin
	Acetylcholine
	Histamine
	Hypocretin/orexin
	Glutamate

GABA  $\gamma$ -amino butyric acid  
<sup>a</sup>Melatonin is a neurohormone

the same wake-promoting neurotransmitters are wake promoting. [2] Over the last few years, several new prescription drugs have been introduced into the market that target one or more of these neurotransmitters and many more are in the pipeline. This chapter discusses the drugs that are used or prescribed for their sedating or stimulant effects. Dopamine agonists are used for the treatment of periodic limb movements and are discussed elsewhere in the book.

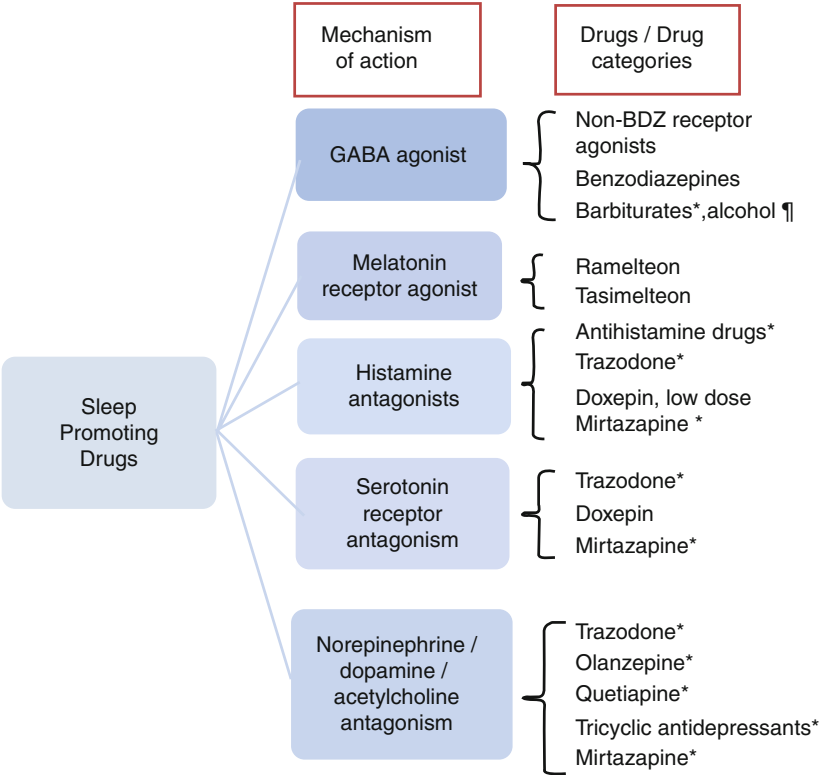
Sleep-Promoting Drugs

The potentiation of GABA or inhibition of wake promoting neurotransmitters produces sedation. Accordingly, sedative action depends on binding of the drug to the corresponding receptor (Fig. 2.1). GABA is the major sleep promoting neurotransmitter ( $\gamma$ (gamma)-amino butyric acid). Drugs that potentiate sleep via GABA act by binding to the GABA<sub>A</sub> receptor [3]. The GABA<sub>A</sub> receptor is a pentameric protein complex regulating a transmembranous chloride channel. It is comprised of five subunits, typically a combination of two alpha, two beta, and one gamma,  $2\alpha$ (alpha)  $2\beta$ (beta)  $1\gamma$ (gamma). Binding of a drug to one or more subunits leads to allosteric changes in the GABA<sub>A</sub> complex with resultant opening of the chloride channel. Negatively charged chloride ions enter into the cell via the open chloride channel inhibiting neuronal activity. The  $\alpha$  (alpha)1 subunit specifically mediates sedation [3].

Additionally, the melatonin receptor agonists that are used as sedatives are discussed. The remaining drugs reviewed in this section are drugs that produce sedation, as a secondary effect via antihistamine, antiserotonin, or antiadrenergic activity, and are used off-label, except for doxepin, Fig. 2.1. The newest agent in development is an orexin/hypocretin antagonist.

Benzodiazepines

Benzodiazepines had been the mainstay of pharmacotherapy for insomnia for the past several decades. Benzodiazepines bind nonselectively to the GABA<sub>A</sub> receptor,



\*Off label use; BDZ Benzodiazepine, only flurazepam, quazepam, estazolam and temazepam are FDA approved for insomnia; MAOI: Monoamine oxidase inhibitors; ¶ Alcohol is commonly self-administered for use as a sedative

**Fig. 2.1** Overview of drugs that are sleep promoting and their site(s) of action

and hence, in addition to sedation, also mediate antianxiety, anticonvulsant, anterograde amnesia, and myorelaxant effects. Benzodiazepines increase sleep duration [4–6] and modify the sleep architecture by slow-wave sleep (SWS) and rapid-eye movement (REM) sleep. They also promote increased sleep spindles. Based on the duration of action, they can be categorized into short-, intermediate-, and long-acting agents (Table 2.2). Benzodiazepines have been associated with a number of dose-dependent adverse effects, including daytime drowsiness due to hangover effect, dizziness, anterograde amnesia, tolerance, drug dependence, and upon withdrawal, rebound insomnia, REM rebound. Withdrawal symptoms, including seizures, following drug cessation [4–6] limit their use. The drugs should be tapered slowly to avoid withdrawal effects. The longer acting drugs produce next day “hang-over” effects due to residual sedation, while the shorter acting drugs are more prone to cause drug dependence, anterograde memory loss, and rebound insomnia.

**Table 2.2** Pharmacokinetics and dosing of benzodiazepines

Generic name	Trade name	Dose mg	Half-life (h)	Peak effect (h)
Long acting (>24 h)				
Flurazepam <sup>a</sup>	Dalmane	0.125–0.6	48–250	0.5–1
Quazepam <sup>a</sup>	Doral	7.5–1.5	41–250	2
Diazepam	Valium	5–10	20–50	1–1.5
Intermediate acting (6–24 h)				
Estazolam <sup>a</sup>	ProSom	1–2	10–24	2
Temazepam <sup>a</sup>	Restoril	7.5–30	3.5–18	1.2–1.6
Lorazepam	Ativan	0.5–2 g	10–20	2–4
Oxazepam	Serax	10–15	5–20	3
Short acting (<6 h)				
Triazolam <sup>a</sup>	Halcion	0.125–0.5	1.5–5.5	1–2

<sup>a</sup>FDA approved agents for chronic insomnia

Benzodiazepines are pregnancy category D or X drugs. Only flurazepam, quazepam, estazolam, and temazepam are FDA approved as hypnotics for the treatment of insomnia; however, other benzodiazepines are routinely used off-label despite lack of adequate data regarding their efficacy and safety (Table 2.2) [7–9].

### ***Nonbenzodiazepine Receptor Agonists (NBRA)***

The search for an ideal agent that specifically targets insomnia led to the development of the nonbenzodiazepine receptor agonists (NBRAs). Unlike the benzodiazepines, the NBRAs have no anxiolytic, myorelaxant, and anticonvulsant properties but have very strong hypnotic properties due to their selective binding to the  $\alpha$ (alpha)1 subunit of the GABA<sub>A</sub> receptor. An ideal therapeutic agent for insomnia should aim to treat both sleep onset and sleep maintenance insomnia without significant residual hangover effects, tolerance, or rebound insomnia upon stopping. The NBRAs were developed keeping these characteristics in mind. The three NBRA agents available in the USA, zolpidem, zaleplon, and eszopiclone are FDA approved for short-term use for insomnia. In addition, zolpidem modified release (Ambien® CR) and eszopiclone are approved for long-term use for up to 6 months for insomnia for sleep maintenance insomnia [10]. The pharmacologic properties of these drugs are presented in Table 2.3. Zopiclone is not available in the US market and is not discussed here. Zolpidem is currently available for use both via oral and sublingual routes. A recent crossover multicenter study revealed that sublingual zolpidem significantly shortened latency to persistent sleep (LPS) by 34% (10.3 min) as compared to oral zolpidem ( $p=0.00$ ) [11].

*Side effects:* Potential side effects of NBRAs are enumerated in Table 2.3. Most frequent adverse events for zolpidem extended-release were headache, anxiety, and somnolence. No rebound effect was observed during the first three nights of discontinuation [12]. In contrast, in a 4-week study of zaleplon and zolpidem in adults



Table 2.3 Pharmacology of NBRAs

Generic name	Zolpidem	Zaleplon	Eszopiclone
Trade name	Ambien	Sonata	Lunesta
Chemical structure	Imidazopyridine	Pyrazolopyrimidine	Cyclopyrrolone (s-isomer)
Elimination half-life	Zolpidem tartrate: 2.6 h (2.9 h elderly) Zolpidem MR: 2.8 h, provides extended plasma concentrations beyond 3 h after administration	1 h	6 h
Drug metabolism	Cytochrome P450	Aldehyde oxidation	Cytochrome P450
Recommended dose	10 mg	10 mg	2–3 mg
Dose adjustment	Elderly or hepatic impairment: 5 mg, (modified release: 6.25 mg)	Elderly: 5 mg	Elderly: 1–2 mg Hepatic impairment: 1 mg
Indication (s)	Short acting: sleep onset sleep onset and maintenance	Sleep onset only	Sleep onset and sleep maintenance
Pregnancy warning	Pregnancy category C	Pregnancy category C	Pregnancy category C
Controlled substance	Schedule IV	Schedule IV	Schedule IV
Drug-drug interaction	CNS suppressants [191] Increased drug levels with inhibitors of CYP3A4 e.g., azole antifungals; decreased drug levels with inducers of CYP3A4 e.g., rifampicin	CNS suppressants [192] Increased drug levels with inhibitors of both aldehyde oxidase and CYP3A4 e.g., cimetidine, erythromycin	CNS suppressants [178] Increased levels with inhibitors of CYP3A4 e.g., itraconazole, ketoconazole, clarithromycin, ritonavir, nelfinavir; decreased drug levels with inducers of CYP3A4 e.g., rifampicin
Adverse effects	Residual sedation, rebound insomnia, complex behaviors Reports of anaphylactoid reaction [191]	Headache, abdominal pain, nausea, dizziness, somnolence [192]	Same as zolpidem In addition, unpleasant taste, dry mouth, somnolence, headache, and dizziness [30]

NBRA nonbenzodiazepine receptor agonists; MR modified release; h hour; CNS central nervous system

with chronic insomnia, significant rebound and withdrawal effects were observed in the zolpidem group [13]. There is little potential for drug dependence with these agents. The incidence of dependence is lower than that of benzodiazepines. In extreme cases, dose increases reached a factor of 30–120 above the recommended doses. The majority of patients demonstrating drug dependence had a history of former drug or alcohol abuse and/or other psychiatric conditions [12].

Patients should be counseled to take these medications as they get into bed and only when they are able to stay in bed a full night (7–8 h) before being active again. In a crossover double-blind administration of zaleplon 10 mg, zolpidem 10 mg, or placebo, healthy subjects were awakened and given medication at times 5, 4, 3, or 2 h before morning awakening, which occurred 8 h after bedtime [14]. Zaleplon was free of residual sedative effects when taken as little as 2 h before waking in normal subjects. In contrast, residual effects of zolpidem were still apparent on objective assessments up to 5 h after nocturnal administration. Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative hypnotic, with amnesia for the event) have been reported with sedative hypnotics, including zolpidem [15]. Although behaviors such as “sleep-driving” may occur with zolpidem tartrate at therapeutic doses, the concomitant use of alcohol and other CNS depressants increases the risk. The drug should be discontinued in patients who report a “sleep-driving” episode. Rare occurrence of angioedema involving zolpidem is listed on the package insert [191]. Zolpidem modified release tablets should not be crushed, divided, or chewed, and should not be taken with or immediately after a meal.

*Efficacy studies:* There are few head-to-head trials comparing the three NBRAs. Clinical placebo-controlled trials investigating efficacy of zolpidem, zaleplon, or eszopiclone have reported on sleep quality and drug effects on sleep architecture. These are presented in below and in Table 2.4 [10–15, 17–35]. Employed adults with chronic insomnia treated with zolpidem extended-release 12.5 mg experienced significantly improved work performance over 24 weeks [26]. There were sustained improvements on sleep with decreased sleep latency, wake time after sleep onset, number of awakenings, increased total sleep time and sleep quality. Ratings of daytime ability to function, alertness and sense of physical well-being, compared to baseline, were also noted after 6 months of eszopiclone [32]. Furthermore, 12 months of nightly treatment with eszopiclone 3 mg was also well tolerated and tolerance was not observed [28]. Additionally, eszopiclone improved CPAP compliance: a short course (24 month) of 3 mg eszopiclone during the first 2 weeks of CPAP improved adherence with 20.8% more nights and for 1.1 h more per night of CPAP use [31]. Long-term nightly use of eszopiclone (3 mg) for primary insomnia enhanced quality of life, reduced work limitations, and reduced global insomnia severity [36]. Eszopiclone was also cost-effective for the treatment of primary insomnia in adults, especially when lost productivity costs were included [37]. Over a 6-month period, eszopiclone use resulted in a net gain of 0.0137 QALYs over placebo at an additional cost of \$67, resulting in an incremental cost per QALY gained of slightly less than \$5,000.

*Comparison with benzodiazepines:* One meta-analysis, comprising of 24 eligible studies with a total study population of 3,909, concluded that due to poor methodological

**Table 2.4** Studies investigating NBRA efficacy

Study design, comparison, author, year	Subject	Dose of active drug	PSG vs. questionnaires	Results: sleep parameters and other measures
RCT/placebo multicenter, parallel group, Elie et al. [13]	N=615, age 42±12.9 y, 18–65 y	Zaleplon, 5, 10, or 20 mg; zolpidem, 10 mg; or placebo, 4 weeks	PSG not done	Sleep questionnaires: Median SL significantly lower with zaleplon, 10 and 20 mg, than with placebo during all 4 weeks of treatment and with zaleplon, 5 mg, for the first 3 weeks. Zolpidem, 10 mg, significantly decreased SL, increased sleep duration, and improved sleep quality. Zaleplon, 20 mg, also significantly increased sleep duration compared with placebo in all but week 3 of the study.
RCT/placebo Fry et al. [18]	N=355, age 40±13 43 y, 18–65	Zaleplon 5, 10, and 20 mg compared to placebo; zolpidem 10 mg as active comparator;4 weeks	Post sleep questionnaires  PSG not done	Rebound insomnia with the zolpidem. No rebound with zaleplon.  Zaleplon 20 mg decreased SL, significant effects on sleep duration, number of awakenings. Zaleplon 10 mg had no effect on number of awakenings. Zolpidem 10 mg significantly improved sleep latency, sleep duration, and sleep quality.
Randomized, multicenter, crossover, Allain et al. [19]	N=53, mean age 52.2 y, 40 and 65 y, primary insomnia	10 mg zolpidem vs. 10 mg zaleplon, 2 consecutive nights with 1 night on each drug	Postsleep questionnaires PSG not done Sleep Questionnaire, visual analogue scale (VAS)	Greater withdrawal symptoms with zolpidem Questionnaire: 62% of patients preferred zolpidem, while 38% preferred zaleplon (p=0.08). The quality of sleep items getting to sleep and quality of sleep were significantly improved after zolpidem (p=0.03 and p<0.0001, respectively). VAS: subjective sleep quality was significantly better after zolpidem (p<0.0001).

(continued)

**Table 2.4** (continued)

Study design, comparison, author, year	Subject	Dose of active drug	PSG vs. questionnaires	Results: sleep parameters and other measures
RCT/placebo multicenter, parallel, Perlis et al. [20]	N = 199, age 41.0 ± 12.8 y, 25–60, primary insomnia	10 mg zolpidem, 3–5 pills/week, 12 weeks	PSG not done Sleep diary	42% decrease in sleep latency; no tolerance, no dose escalation, and no evidence of rebound insomnia. Fifty two percent reduction in number of awakenings, a 55% decrease in wake time after sleep onset, and a 27% increase in total sleep time.
RCT/placebo multicenter, parallel, Krystal et al. [21]	N = 1018, age 18–64 y, primary insomnia	12.5 mg zolpidem MR, 24 weeks, 3–7 day run – in and 7 day run-out phase	PSG not done Sleep questionnaire	Zolpidem MR was significantly superior to placebo with improved TST, WASO and SL ( $p \leq 0.0014$ ). Patient's global impression scores significantly favorable for zolpidem MR.
RCT/placebo multicenter, parallel, Krystal et al. [22]	N = 593, age 21–69 y, primary insomnia	3 mg eszopiclone, 6 months	PSG not done Interactive voice-response system (IVRS)	At 6 month- drug vs. placebo, SL: 47.0 vs. 63 min <sup>a</sup> ; WASO 44 vs. 48 min <sup>a</sup> ; at 6 month-TST: 378 vs. 339 min <sup>a</sup> ; awakenings/night: 1.9 vs. 2.6 <sup>a</sup> ; sleep quality and alertness were improved <sup>a</sup> .
RCT/placebo multicenter, parallel, Zammit et al. [27]	N = 308, age 21–64, primary insomnia	2–3 mg eszopiclone, 44 nights	PSG and patient reports	2 mg dose did not significantly improve sleep maintenance 3 mg had significantly less time to sleep onset ( $p < 0.0001$ ), more total sleep time and sleep efficiency ( $p < 0.0001$ ), better sleep maintenance ( $p < 0.01$ ), and enhanced quality and depth of sleep ( $p < 0.05$ ) across the double-blind period compared with placebo. Average SL was 33.0 min for placebo and 23.0 minutes and 18.0 min, for the 2 and 3 mg doses respectively ( $p < 0.01$ ). There was no evidence of tolerance or rebound insomnia after therapy discontinuation. Digit-symbol substitution test showed no decrement in psychomotor performance next day.

RCT/placebo multicenter, parallel, Scharf et al. [29]	N=231, age 65–85 y, primary insomnia	1–2 mg eszopiclone, 2 week	PSG not done IVRS	Patient-reported data via IVRS at week 2, drug vs. placebo: 1 mg; SL, min: 43.3 vs. 65 <sup>a</sup> ; 2 mg: 48 vs. 65 <sup>a</sup> ; WASO, min: 1 mg: 63 vs. 67 <sup>a</sup> ; the 2 mg dose had similar effects on WASO and awakenings at night TST, min: 1 mg dose: 357 vs. 349 <sup>a</sup> ; 2 mg dose: 379.1 vs. 349 <sup>a</sup> .
RCT/placebo multicenter, parallel, McCall et al. [30]	N=264, age 64–86 y, primary insomnia	2 mg eszopiclone, 2 weeks	PSG measurements and patient report	Patient report: LPS, min: 15 vs. –30 <sup>a</sup> ; WASO, min: 82 vs. 91 <sup>a</sup> ; number of awakenings unchanged; PSG: TST, min: 385 vs. 358 <sup>a</sup> ; SE, %: 80 vs. 75 <sup>a</sup> ; increased stage 2 sleep, %: 2.3 vs. –0.1; no change in REM.SWS compared with placebo; SL min: 30 vs. 41 <sup>a</sup> ; WASO, min: 75 vs. 91 <sup>a</sup> ; TST, min: 387 vs. 324 <sup>a</sup> ; ISI score: –6 vs. –4 <sup>a</sup> ; fewer naps with drug vs. placebo.
RCT/placebo multicenter, crossover study, Erman et al. [31]	N=65, age 21–64 y, primary insomnia	Eszopiclone 1, 2, 2.5, or 3 mg vs. zolpidem 10 mg vs. placebo; two nights each	PSG measurements	All active treatments significantly reduced median LPS relative to placebo by 42–55% (LPS 13–16 min with drug); higher SE with eszopiclone 2, 2.5, and 3 mg, and zolpidem 10 mg compared with eszopiclone 1 mg; WASO was significantly lower for eszopiclone 3 mg but not for zolpidem 10 mg or the other eszopiclone doses.
RCT/placebo AncoI Israel et al.[34], Phase IV trial	N=388, age 65–85 y, primary insomnia, comorbid depression, dementia	2 mg eszopiclone, 12 weeks study, 2-week run out, 4-week follow-up	PSG not performed Electronic sleep/wake diaries	Electronic sleep/wake diaries TST: 12 wks vs. baseline: 360.08 vs. 297 min; SL: 24.62 vs. 19.92 min; WASO decrease of 36 min

(continued)

Table 2.4 (continued)

Study design, comparison, author, year	Subject	Dose of active drug	PSG vs. questionnaires	Results: sleep parameters and other measures
RCT, crossover study, placebo, Joffe et al. [35]	N = 59, age 40–65 y, peri/postmenopausal women, menopause-associated insomnia	3 mg eszopiclone, 11 weeks	PSG not performed  Sleep diary	Sleep diary: difference between eszopiclone and placebo. TST 66.5 min <sup>a</sup> ; SL 17.8 min <sup>a</sup> ; SE: 15% <sup>a</sup> , WASO: 37.7 min <sup>a</sup> . Reduced ISI scores by 8.7 points <sup>a</sup> . Eszopiclone improved all sleep parameters, depressive symptoms, anxiety symptoms, quality of life, and nighttime but not daytime hot flashes.

PSG polysomnography; RCT randomized controlled trial; N number; y year; wks weeks; LPS latency to persistent sleep; TST total sleep time; SE sleep efficiency; AHI apnea hypopnea index; REM rapid-eye movement sleep; SWS slow wave sleep; ISI insomnia severity index score; WASO wake time after sleep onset; SL sleep latency; IVRS interactive voice response system; VAS visual analogue scale; MR modified release, % percentage

<sup>a</sup> p<0.05, drug vs. placebo

quality, secondary to insufficient or inappropriately reported data, a clear distinction between benzodiazepines and NBRA could not be made apart from those arising from pharmacokinetic properties [38]. For a review of comparisons of NBRAs with benzodiazepines, the reader is referred to detailed meta-analysis and reviews completed elsewhere [7, 8, 38, 39].

### ***Barbiturates Derivatives***

Barbiturates and their derivatives (i.e., glutethimide, chloral hydrate) also potentiate GABA and have been used as sedatives. They are no longer in use as sedatives due to risk of significant adverse effects, development of tolerance, and dependence with long-term use [40].

### ***Melatonin Receptor Agonists***

#### **Ramelteon**

Ramelteon is a synthetic analog of melatonin and a melatonin receptor agonist. Ramelteon acts by binding selectively to the MT<sub>1</sub> and MT<sub>2</sub> receptors, two G-protein coupled receptors [41]. The melatonin MT<sub>1</sub>-receptor and MT<sub>2</sub>-receptor mRNA in the suprachiasmatic nucleus (SCN) mediate SCN firing by melatonin [42] and the phase-shifting effects of melatonin on circadian rhythms [43, 44], respectively. Ramelteon's positive effects on sleep are associated with an attenuation of the circadian rise in core body temperature and an increase in skin temperature [45]. The magnitude of the increase in skin temperature is correlated with a faster latency to sleep with ramelteon.

*Pharmacologic characteristics:* Peak concentration of the drug is reached in 0.75 h when fasting [46]. It should be taken on an empty stomach as peak concentrations are reduced by 25% after a meal. It undergoes a high first-pass metabolism in the liver [47, 48]. Elimination half-life of ramelteon at an 8-mg dosage is 2–5 h [46]. Clearance is reduced in the elderly due to a longer half-life in the elderly age group 60–79 year (1.9 h) vs. younger age group (1.3 h) [48]. Studies suggest a flat dose–response across dosages of 4–32 mg [49]. The recommended dose is 8 mg at bedtime [46].

Ramelteon has not been shown to produce dependence and has no potential for abuse unlike the GABAergic drugs [50]. In a study of substance abusers given ramelteon or triazolam, ramelteon did not demonstrate any potential for abuse liability [50] or withdrawal. It is currently the only nonscheduled prescription drug that is FDA approved for the treatment of sleep-onset insomnia.

*Drug–drug interactions:* There is significant drug interaction with fluvoxamine co-administration, resulting in a more than 100-fold increase in the levels of ramelteon [51] and the two drugs should not be combined. Ketoconazole (CYP3A4 inhibitor) increases ramelteon levels whereas rifampin (CYP enzyme inducer) decreases

effects of ramelteon [46]. Doxepin and fluconazole also increase systemic exposure of ramelteon [46].

*Drug efficacy and tolerance:* Overall, melatonin reduced sleep onset latency with no consistent or clinically appreciable effects on measures of sleep maintenance. Several trials have evaluated the efficacy of ramelteon on sleep onset and maintenance [16, 49–63], see Table 2.5. Psychomotor performance was not reduced the next day or during the night with ramelteon [49, 52], and there were no significant next-morning residual effects [52, 58, 59] observed via Digit Symbol Substitution Test (DSST), memory recall tests (immediate and delayed), visual analog scales (feelings and mood), and Postsleep Questionnaire (level of alertness and ability to concentrate) [52]. In a 6-month efficacy study, there was no decrease in the morning level of alertness or the ability to concentrate throughout the study duration. There was no rebound insomnia after discontinuation of the drug [54]. Similarly, there was no evidence of significant rebound insomnia or withdrawal effects following treatment discontinuation after 5 week in older adults [53]. Ramelteon did not impair middle-of-the-night balance, mobility, or memory relative to placebo [16]. Ramelteon also did not produce oxygen desaturation or increase apnea–hypopnea index in subjects with mild to severe COPD [60, 61]. It is a pregnancy category C drug.

Incidentally, ramelteon’s new drug application was recently denied in Europe based on lack of evidence for effectiveness. The evaluation committee was “concerned that the company had not demonstrated a long-term effectiveness of ramelteon and that the benefit of ramelteon had not been sufficiently demonstrated and any benefits did not outweigh the identified risks.”

Data regarding ramelteon’s circadian phase shifting efficacy are limited. Ramelteon reentrained the light–dark cycle in an animal study [177] and also in recent studies in healthy humans with phase advance [187, 188]. Chronobiotic effect of ramelteon was affected by level of light exposure. Further evaluations in individuals with circadian rhythm sleep disorders are warranted.

*Side effects:* The incidence of adverse effects was low. The most commonly reported treatment-emergent adverse effects were dizziness (ramelteon, 8.9%; placebo, 7.1%), dysgeusia (ramelteon, 7.0%; placebo, 2.9%), myalgia (ramelteon, 6.4%; placebo, 3.5%), and headache (ramelteon, 5.1%; placebo, 5.9%) [59, 60]. Angioedema and anaphylaxis have been reported [46, 60, 61]. Long-term exposure to ramelteon 16 mg, a potent melatonin receptor agonist, resulted in mild, transient increase in prolactin, in women only, with no measurable reproductive effects [51].

## **Tasimelteon**

Tasimelteon, another melatonin MT1/MT2 agonist studied in a phase III trial demonstrated that in a model of abrupt advance in sleep time, the drug produced improved sleep latency, sleep efficiency, and wake after sleep onset [190]. The frequency of adverse events was similar between tasimelteon and placebo.



**Table 2.5** Studies investigating ramelteon efficacy

Study design, comparison, author, year	Subject	Dose of active drug	PSG vs. questionnaires	Results: sleep parameters and other measures
RCT/placebo multicenter, Roth et al. [56]	N = 375, age 35–60 y, healthy adults, transient insomnia, one night	16 and 64 mg	PSG, postsleep questionnaire, digit symbol substitution test (DSST)	PSG LPS, min, – 8 mg: 14 vs. 24 <sup>a</sup> ; 16 mg: 22 vs. 31 <sup>a</sup> TST, min, – 8 mg: 25 vs. 41 <sup>a</sup> ; 16 mg: 422 vs. 411 <sup>a</sup> There were no significant differences among the groups for DSST scores, suggestive of no residual sleepiness.
RCT/placebo multicenter, crossover, Erman et al. [49]	N = 107, age 18–64 y, primary insomnia, two nights at each dose	4, 8, 16, and 32 mg	PSG, postsleep questionnaire, VAS, DSST	All tested doses of Ramelteon resulted in statistically significant reductions in PSG LPS (by approximately 7–8 min) and increases in TST (by approximately 2–8 min). No differences in WASO compared with placebo. No next-day residual effects noted at any dose There were no differences in adverse events (headache, somnolence, sore throat).
RCT/placebo multicenter, Zammit et al. [58]	N = 405, age 18–64 y, primary insomnia	8 and 16 mg, 5 weeks	PSG, postsleep questionnaire, VAS, DSST	PSG LPS, min, – 8 mg: 32 vs. 47.9 <sup>a</sup> at week 1; maintained at weeks 3 and 5 PSG TST, min, – 8 mg: 394 vs. 375 <sup>a</sup> at week 1; maintained at weeks 3 and 5 Similar effects were noted with the 16-mg dose. Wake time after sleep onset and number of awakenings were not significantly different with ramelteon 8 or 16 mg. No effect on sleep architecture, next-day psychomotor tasks, alertness, or ability to concentrate. No withdrawal or rebound effects were observed.

(continued)

Table 2.5 (continued)

Study design, comparison, author, year	Subject	Dose of active drug	PSG vs. questionnaires	Results: sleep parameters and other measures
RCT, placebo, multicenter, Roth et al. [53]	N=829, age >or= 64 (64–93 y), primary insomnia	4 and 8 mg, 5 weeks	PSG, sleep diary	PSG SL, min, – 4 mg: 70 vs. 78 <sup>a</sup> at week 1; maintained at week 5 PSG SL, min, – 8 mg: 70 vs. 78 <sup>a</sup> at week 1; maintained at weeks 3 and 5 PSG TST, min – 4 mg: 324 vs. 313 <sup>a</sup> at week 1; 336 vs. 324 <sup>a</sup> at week 3 PSG TST, min – 8 mg: 321 vs. 314 <sup>a</sup> at week 1; 8 mg: 332 vs. 324 at week 3; no differences at week 5. No rebound insomnia or withdrawal effects were noted.
RCT, crossover study placebo, multicenter, Roth et al. [52]	N=100, age 65–83 y, primary insomnia, two nights each at each dose	4 and 8 mg, 9 weeks	PSG, postsleep questionnaire, VAS, DSST	PSG LPS, min, – 4 mg: 28.7 vs. 38.4 <sup>a</sup> PSG LPS, min, – 8 mg: 30.8 min vs. 38.4 <sup>a</sup> Total sleep time ( $p=0.036$ and $p=0.007$ , respectively) and sleep efficiency ( $p=0.037$ and $p=0.007$ , respectively) were also significantly improved with ramelteon 4 and 8 mg, respectively. No residual daytime effect noted.
RCT/placebo multicenter, posthoc analysis, Mini et al. [63]	N=157, mean age 72.7 y, severe sleep-onset difficulty in primary insomnia (subjective sleep latency >60 min)	8 mg, 5 weeks	Sleep diary	Reductions in subjective SL, min from baseline: –23 vs. –7.5 at week 1; sustained at week 3 and 5
RCT, multicenter, placebo, Mayer et al. [54]	N=451, age 18–79 (mean 46) y, primary insomnia	8 mg, 6 month	PSG and morning questionnaires, DSST, VAS	Reductions in LPS, min – week 1: 381 vs. 365 <sup>a</sup> ; significant decreases were observed at week 1 and months 1, 3, 5, and 6 ( $p<0.05$ ). No significant change in TST, subjective number of awakenings and sleep quality. No next-day residual effects. No withdrawal symptoms or rebound insomnia were detected after discontinuation.

For annotations, see Table 2.3 and 2.4

<sup>a</sup>  $p<0.05$ , drug vs. placebo

## ***Melatonin***

Melatonin is a neurohormone of the pineal gland that is modulated by the SCN of the hypothalamus. Regulation of melatonin synthesis by the SCN determines the circadian rhythm of sleep and wakefulness [1]. Synthetic melatonin is available over the counter as a “nutritional supplement.” Melatonin has hypnotic effects and in doses of 0.1–12 mg has been used as a sedating agent, for the treatment of sleep-onset insomnia and insomnia related to jet lag, shift-work sleep disorder (SWSD), and delayed sleep phase disorder, but with variable efficacy. The reader is referred to excellent systematic reviews [64–68]. Melatonin was effective in entraining free-running blind individuals [69]. Melatonin may also be effective in the management of REM sleep behavior disorder [70]. The drug has few side effects including headache, dizziness, nausea, or abdominal cramps [71]. Purity of the drug must be ascertained prior to its use.

## ***Antidepressants and Antipsychotics***

A number of antidepressants cause sedation as a secondary effect and practitioners have used these drugs off-label to treat insomnia. This is despite the fact that there are very few controlled, short- or long-term studies to validate their safety and efficacy for use in patients with primary insomnia and these drugs, other than the recently approved low-dose doxepin, cannot be recommended as first-line pharmacotherapy in primary insomnia. Other antidepressants may produce insomnia as described below.

### **Trazodone**

Trazodone probably produces sedation by blocking the 5HT-2a/2c receptor. Prior to the introduction of NBRAs in the 1990s, trazodone was the most highly prescribed drug for insomnia. This is despite the fact that the efficacy of trazodone for treatment of insomnia had been studied in only small populations for insomnia in depressed individuals, usually with limited subjective sleep evaluations of sleep duration, sleep latency, or nocturnal awakenings and without objective polysomnographic data. In one such study ( $N=17$ ), trazodone was reportedly effective for patients with insomnia related to antidepressant (fluoxetine or bupropion) use, with increased Pittsburgh index of sleep duration but unchanged Pittsburgh index measures of sleep efficiency [72]. In six depressed patients with significant sleep disturbances in an 8-week single-blind study design, trazodone (150–400 mg) produced a 44% improvement in persistent sleep latency, total sleep time, and sleep efficiency with a doubling of stage IV sleep [73]. There was no change in percentage of REM; however, REM latency increased 28%. Trazodone 100 mg given over

7 days increased TST and SWS and decreased awakenings in patients with sleep disruption due to antidepressants compared with placebo [74] (Tables 2.6 and 2.7). In addition, data in nondepressed patients is limited. In a 2-week, parallel group study in nondepressed primary insomniacs, comparing trazodone 50 mg and zolpidem 10 mg, only zolpidem maintained a significantly shorter sleep latency than the placebo group, with no differences in sleep duration among the groups at week 2 [75].

*Side effects:* Potential adverse reactions include dizziness, dry mouth, nausea/vomiting, constipation, headache, orthostatic hypotension, ventricular arrhythmias/torsades de pointes [76, 77], and, rarely, priapism [78]. This should caution physicians against routine use of trazodone for insomnia, especially in the elderly [79, 80].

### Tricyclic Antidepressants (TCA)

Tricyclic Antidepressant (TCA) agents produce sedation via their antihistaminergic and anticholinergic properties [81–85]. These are presented in Tables 2.6 and 2.7. The TCA are limited by their anticholinergic side effects. Clomipramine, amitriptyline, and doxepin are more sedating than other TCAs, while desipramine is the least sedating. These drugs are linked with increased periodic leg movements. However, based on efficacy and safety studies, the FDA recently approved low-dose doxepin (Silenor® 3, 6 mg) as the first antidepressant with an indication for the treatment of sleep maintenance insomnia [86–89]. The drug has high specificity and affinity to the histamine H(1) receptor and this property of doxepin makes it a good sedative at low doses without the concomitant major anticholinergic side effects.

### SSRI and SNRI

SSRIs may be associated with daytime insomnia or sedation, depending on their effect on different serotonin (5-hydroxytryptamine [5-HT]) receptor subtypes. They suppress REM sleep and delay REM latency. The serotonin and norepinephrine reuptake inhibitor (SNRI), e.g., venlafaxine and duloxetine also produce sleep fragmentation, insomnia, and suppress REM sleep [81] (Tables 2.6 and 2.7). Stimulation of the 5-HT<sub>2</sub> receptors may contribute to insomnia and the observed changes in sleep architecture with SSRIs or SNRI. However, daytime sedation has also been observed with fluoxetine [90]. The SSRIs may have paradoxical daytime sedating effect, with fluvoxamine being the most sedating. SSRIs have been associated with increased eye movements in NREM sleep [91, 92] and periodic leg movements on polysomnography. They have also been associated with increased REM sleep without atonia [93]. Two excellent reviews have addressed the variable effects of antidepressants on sleep [81, 94]. Side effects of SSRIs included gastrointestinal adverse effects (nausea and diarrhea), headache, dizziness, hypotension, agitation, insomnia and tremor, weight gain, and sexual dysfunction. Compared to TCAs, SSRIs have fewer anticholinergic effects. Of the SSRIs, paroxetine is pregnancy class D and the rest are pregnancy class D.

**Table 2.6** Overview of the site of action and effect on sleep architecture of sedatives and psychoactive drugs

Drug	Mechanism of action	Effect on sleep duration, sleep latency and sleep architecture
Benzodiazepines	GABA <sub>A</sub> receptor-nonspecific binding	Increased TST, short SOL, decreased SWS, and decreased%REM, increased stage 2, pseudospindles
NBRAs	GABA <sub>A</sub> - $\alpha$ (alpha)1 subunit	Increased TST, increased sleep efficiency, short SOL, unchanged sleep architecture
Barbiturates	Opens chloride channel	Increased TST, short SOL, decreased SWS, and decreased%REM
Valerian	Agonist:GABA receptor, A(1) adenosine or 5-HT <sub>2a</sub>	Decreased SOL, increased SWS (after prolonged use), no change in REM sleep
Gabapentin	Mechanism for somnolence is not clear in humans	Increased SE, increased SWS%, decrease in arousals, and stage 1 sleep
Ramelteon	MT1/MT2 receptor agonist	Increased TST, short SOL, no changes in SWS, REM sleep percentages or WASO
Almorexant <sup>a</sup>	Orexin receptor antagonist	Results pending, preliminary results show reduced WASO
Mirtazapine <sup>b</sup>	5-HT <sub>2</sub> /5-HT <sub>3</sub> antagonist, central alpha2-adrenergic antagonist, H1 antagonist	Increased TST and SE, decreased SOL, no significant change in REM [179]. In another study [180], mirtazapine increased total SWS and the SWS in the first sleep cycle, but not SWS in the second sleep cycle, increased REM latency, the duration of the first REM episode and decreased the number of REM episodes. Reduced WASO
Trazodone <sup>b</sup>	specific inhibitor of synaptosomal reuptake of serotonin, 5HT <sub>2</sub> and 5HT <sub>3</sub> antagonist, H1 antagonist, alpha 1 blockade	Decreased stage 2, increased SWS, slight decrease/increase in REM sleep
Doxepin, low dose (6 mg)	Selective H1 receptor antagonist, alpha 1 antagonist	Increased TST and SE, decreased SOL and WASO/awakening, increased stage 2, increased stage N2 and N3, decreased%REM sleep
Bupropion <sup>b</sup>	Dopamine and norepinephrine reuptake inhibition	Increased REM sleep%, decreased periodic limb movements, insomnia
TCA	H1 antagonist, antialpha1, antiach	Increased SE, decreased SOL, decreased REM sleep% except with trimipramine (see text), increased periodic limb movements in sleep
SSRI: paroxetine, fluoxetine, citalopram	Serotonin reuptake inhibitor	Variable effects on sleep continuity with majority causing sleep fragmentation. Also decreased REM sleep% and increased REM latency, increased periodic limb movements in sleep, "prozac" eyes
SNRI: venlafaxine and duloxetine	5-HT and norepinephrine reuptake inhibitor	Insomnia, decreased REM sleep%, increased periodic limb movements in sleep

(continued)

**Table 2.6** (continued)

Drug	Mechanism of action	Effect on sleep duration, sleep latency and sleep architecture
MAOI	5-HT and NE reuptake blocker, antiACh and H1 antagonist	Decreased SOL, decreased REM sleep%, increased periodic limb movements in sleep, decreased sleep continuity
Quetiapine	5-HT <sub>1A</sub> , 5-HT <sub>2</sub> , dopamine (D <sub>1</sub> and D <sub>2</sub> ), H1 antagonist and adrenergic $\alpha$ (alpha) 1 and $\alpha$ (alpha) 2 receptors antagonist [181]	Increased TST, SE, unchanged SOL [182] Increased stage 2 duration @ 2–4 days; unchanged at 3–4 weeks, unchanged SWS and decreased duration in REM sleep @ 2–4 days, but unchanged @ 3–4 weeks Quetiapine increased leg movements in sleep [182]
Olanzapine	H1 antagonist, anti-5-HT <sub>2</sub> , antialpha1, antiACh, antidopaminergic	Increased TST, SE and SWS; variable effect on REM; may acutely increase REM density
Ziprasidone	H1 antagonist, anti-5-HT <sub>2</sub> , antialpha1, antiACh, antidopaminergic	Increased TST, SE and SWS; suppressed REM sleep with prolonged REM latency
Risperidone	Anti-5-HT <sub>2</sub> , anti alpha1, antidopaminergic	Suppressed REM and prolonged REM latency
Nonselective antihistamines (H1)	H1 antagonist, antiACh	Increased sleep efficiency, unchanged SWS and REM%, tolerance develops early to the sedating effect

For annotations, see Table 2.4. See text for other references

*AntiACh* anticholinergic; *H1* histamine-1 receptor; *5-HT* serotonin; *TCA* tricyclic antidepressants; *MAOI* monoamine oxidase inhibitor; *SSRI* selective serotonin reuptake inhibitor; *SNRI* serotonin norepinephrine reuptake inhibitor

<sup>a</sup>Drug is currently undergoing clinical trials

<sup>b</sup>The effectiveness of these drugs on sleep was studied in individuals with major depression

**Table 2.7** Drugs that modify SWS and REM sleep percentages

Increase REM	Decrease REM	Increase SWS	Decrease SWS
Bupropion±	Benzodiazepines	Gabapentin	Benzodiazepines
Trazodone±	Barbiturates	Pregabalin	Barbiturates
Sodium oxybate	TCA	Tiagabine	
	MAOI	Lithium	
	SSRI	Mirtazapine	
	Venlafaxine	Trazodone	
	Duloxetine	Olanzapine	
	Bupropion±	Ziprasidone	
	Trazodone±	Risperidone	
	Traditional antipsychotics, e.g., Haldol	Sodium oxybate	
	Risperidone	Valerian	
	Ziprasidone		

For annotations, see Tables 2.4 and 2.6; and text; ± variable effect on sleep in different studies. See references [81, 85, 96, 97, 99]

## Other Antidepressants

Antidepressants with 5HT<sub>2</sub>, 5HT<sub>3</sub>, and alpha<sub>2</sub> receptor blockade such as mirtazapine improve sleep continuity and may therefore be used for depressed patients with insomnia [84, 85]. Bupropion is a dopamine and norepinephrine reuptake inhibitor. Unlike the antidepressants listed earlier, it may decrease periodic limb movements and also produce insomnia. The monoamine oxidase inhibitors (MAOI) block the activity of monoamine oxidase, an enzyme which breaks down serotonin, norepinephrine, and dopamine. Thus, these drugs raise the brain levels of these neurotransmitters and produce sleep fragmentation. Side effects of MAOI include orthostatic hypotension, headache, weight gain, and insomnia. When on MAOI, ingestion of foods containing the amino acids with tyramine or tyrosine may lead to a life-threatening hypertensive crisis.

## Antipsychotic Agents

Both the traditional and atypical antipsychotics are sedating due to their antagonism of dopaminergic, histaminergic, serotonergic,  $\alpha$ (alpha)1-adrenergic systems [95] (Table 2.6). There are no consistent effects of the traditional antipsychotics on sleep architecture in healthy individuals, but overall they increased TST and SE, and increased REM latency in schizophrenic patients [96]. The atypical antipsychotics have been evaluated in a nonsystematic fashion in small groups of healthy individuals for their effects on sleep [97]. They increased TST and sleep efficiency except for risperidone that showed minimal effect. Ziprasidone, risperidone, and olanzapine increased SWS sleep [97, 98]. Risperidone and ziprasidone suppressed REM sleep and tended to prolong REM latency. Variable effect on REM sleep was noted in different studies with olanzapine. Olanzapine may increase REM density acutely [96]. Quetiapine increased TST and SE but did not have a lasting effect on REM sleep. While most of the antipsychotics are sedating, aripiprazole is the least sedating [97]. Periodic limb movements, RLS, and weight gain have been observed with both the traditional and atypical antipsychotics likely related to their antidopaminergic properties [97]. There also case reports of nocturnal eating and somnambulism [96].

## Other Sedating Drugs

Antihistamines such as diphenhydramine and doxylamine are associated with subjective drowsiness and reduced sleep latency but tolerance develops within 2 weeks of use. Valerian is a plant extract with GABA activity that shortens sleep latency and improves sleep efficiency [99]. Gabapentin has been associated with reduced periodic leg movements during sleep in patients with restless leg syndrome, with increased total sleep time, sleep efficiency, and slow wave sleep, and decreased stage 1 sleep [100]. The mechanism of action of gabapentin on sleep is not clear.

## ***Newer Sedatives Under Development***

### **Almorexant**

Orexin/hypocretin stabilizes wakefulness and is implicated in the pathophysiology of narcolepsy [1]. The administration of an orexin/hypocretin antagonist in animal models and humans decreased sleep time. Almorexant and other orexin/hypocretin antagonists are novel drug types under development and undergoing phase II and III clinical trials in patients with insomnia. Almorexant is an orally active dual OX1 and OX2 receptor antagonist that readily crosses the blood–brain barrier. Preclinical studies and phase I clinical trials have demonstrated that almorexant decreases alertness and increases sleep in healthy rats, dogs, and humans when administered during the active phase of the circadian cycle. In phase I trials, almorexant increased sleep efficiency ( $p < 0.001$ ). There was also improved mean SE (85.4 vs. 71.0%), LPS (36.2 vs. 54.2 min), WASO (40.0 vs. 94.0 min), latency to REM (76.6 vs. 121.9 min), and percentage of REM (19.2 vs. 16.2%) with no effects on next-day performance [101]. No significant toxicological or safety concerns were noted, however, concerns for drug safety were recently reported from a phase III trial. RESTORA 1 (REstore physiological Sleep with The Orexin Receptor antagonist Almorexant) was a (non-US) multicenter, double-blind, randomized, placebo-controlled, active reference (zolpidem), parallel-group polysomnography study to evaluate efficacy and safety of 16-day oral administration of almorexant 200 and 100 mg in adult 709 patients with chronic primary insomnia. RESTORA 1 met its primary endpoint, with significant superiority of almorexant over placebo on objective and subjective wake after sleep onset (WASO). Detailed results from this study are pending. Phase III clinical trials in the USA will be soon underway.

### **Agomelatine**

Agomelatine is a MT1 and MT2 receptor agonist like ramelteon and also has 5-HT<sub>2C</sub> receptor antagonist properties. This has allowed it to be used as a novel agent for the treatment of depression along with an effect on the sleep–wake cycle [102]. Majority of the published literature focuses on its use as an antidepressant. These studies observed the positive impact of the drug on sleep in individuals with major depression. Polysomnography findings after treatment with agomelatine showed an improvement in sleep architecture [103]. There were significant improvements in sleep efficiency, SWS, and the distribution of delta activity throughout the night, but no change in the amount or latency of REM sleep. SWS was resynchronized and distributed to the first sleep cycle of the night. There was a significant increase in the duration of SWS (stages 3 and 4), from  $66 \pm 20$  min to  $80 \pm 20$  min at 6 weeks ( $p < 0.02$  compared with baseline) together with an increase in the delta ratio (from  $0.88 \pm 0.35$  to  $1.16 \pm 0.57$  at 6 weeks,  $p < 0.007$ ). Administration of agomelatine (50 mg) or placebo for a period of 15 days caused phase advances of an average of



2 h in the temperature profile as well as in the temporal organization of cortisol secretion [104], suggesting that agomelatine may also be useful as a chronobiotic agent. Further studies regarding its effects on sleep are warranted.

## **Stimulants/Wake-Promoting Drugs**

This section discusses amphetamine-like stimulants, modafinil, armodafinil, and sodium oxybate. In contrast to the sedatives, the wake promoters act via activation of the noradrenergic, dopaminergic, and/or serotonergic systems. Table 2.8 outlines the mechanisms, pharmacology, and the FDA-approved indications for these agents.

### ***Amphetamine-Like Substances***

Amphetamines act by blocking the reuptake and enhancing the release of norepinephrine, dopamine, and serotonin [105]. Methylphenidate 20 mg reduced REM sleep, prolonged REM latency, increased sleep latency, and reduced TST [106]. Data on the efficacy of these agents as wake-promoting drugs are limited. Side effects include headaches, irritability, nervousness or tremors, psychosis, anorexia, insomnia, gastrointestinal complaints, dyskinesias, and palpitations. Methylphenidate and dextroamphetamine are controlled substances that are FDA pregnancy category C drugs. Dextroamphetamine is now approved for treatment of narcolepsy. The drugs are contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, history of drug abuse, or with administration of MAO inhibitors. A “black box” warning emphasized that amphetamines have a high potential for abuse.

### ***Modafinil***

Modafinil is a nonamphetamine wake-promoting agent that is FDA indicated for the treatment of excessive daytime sleepiness in narcolepsy, SWSD, and in patients with obstructive sleep apnea (OSA) with residual daytime sleepiness on adequate positive airway pressure therapy (PAP) (Table 2.8). The exact mechanism of action of modafinil is not well understood. Studies have proposed different mechanisms [107]. Modafinil may act by binding to the dopamine transporter [108], inhibiting dopamine reuptake and activating dopamine receptors or via activation of histaminergic neurons [109]. Modafinil is effective in hypocretin (orexin) knockout animals indicating that hypocretin is not needed to mediate its effects [110]. Modafinil selectively activated wake-generating sites in the hypothalamus as displayed by increased FOS immunoreactivity in the tuberomammillary nucleus and hypocretin neurons of

**Table 2.8** Wake-promoting drugs

Drug	Mechanism of action	Dose of active drug	Side effects	PSG/MSLT/MWT	Other comments
Amphetamines: Methamphetamine (Desoxyn®) Dextroamphetamine (Dexedrine®)	Increased monoamine release and increased extracellular dopamine and norepinephrine availability	5–20 mg twice a day 5–30 mg bid or 10 mg SR qam with 10–20 mg qpm	Insomnia, restlessness, tachycardia, hypertension, dizziness, diarrhea, psychosis (rare) Nervousness, insomnia, anorexia, nausea, palpitations, dizziness, hypertension, headache	Amphetamines promote wakefulness by blocking the reuptake and increasing the release of dopamine, norepinephrine, and serotonin in the central nervous system –this reduce TST, SWS and REM sleep	Amphetamines are federally controlled substance Schedule II drugs. Methylphenidate and dextroamphetamine are FDA approved for narcolepsy and ADHD [183]. Often prescribed as first-line agents for therapy of excessive daytime sleepiness in narcolepsy
Methylphenidate (Concerta®, Ritalin®)	Blocks reuptake of dopamine, norepinephrine and serotonin	10–30 mg bid, or 20 mg SR qam with 10–20 mg qpm			
Modafinil (Provigil®)	Exact mechanism is not known (see text)	100–400 mg or 200 mg bid Peak concentration: 2–4 h Reduce dosing in hepatic impairment and elderly Drug interactions: reduced levels of oral contraceptive, cyclosporine with the drug; increased levels of diazepam, phenytoin and propranolol	Common: headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia. Less common: chest pain hypertension, tachycardia, precaution: reports of Stevens-Johnson Syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms, multiorgan hypersensitivity reaction, angioedema	No change in sleep latency, sleep architecture. Improved day time functioning and reduced daytime sleepiness	Federally controlled substance Schedule IV drug. FDA approved use in adults, for excessive sleepiness associated with narcolepsy, shift work sleep disorder, obstructive sleep apnea (as an adjunct to adequate PAP use)

Amodafinil (Nuvigil®) (R-modafinil) is the longer acting R isomer of modafinil	Similar to modafinil	Narcolepsy and OSA: 150 or 250 mg qam SWD: 150 mg given daily 1 h prior to the start of the work shift	Common: headache, nausea, dizziness, and insomnia. Less common: dyspepsia, palpitation, rash, increased liver enzymes	No changes in sleep latency, sleep efficiency, arousals, WASO, or sleep staging	Federally controlled substance Schedule IV drug. Indications are same as for modafinil
Sodium oxybate (Xyrem®)	GHB receptors 1 GABA <sub>B</sub> receptors 2	4.5–9 g nightly at bedtime; recommended starting at 4.5 g/night divided into two equal doses, adjusted up to a maximum of 9 g/night in increments of 1.5 g/night at 1- to 2-week intervals  Reduce the starting dose of sodium oxybate by one-half in patients with liver dysfunction	Common: headache (22%), nausea (21%), dizziness (17%), nasopharyngitis (8%), somnolence (8%), vomiting (8%), and urinary incontinence (7%)  Also noted: confusion, depression, sleepwalking, psychosis, paranoia, hallucinations, and agitation, tremor, fall, hypertension	Increase in slow-wave sleep duration and delta power, and decrease in REM sleep duration and nocturnal increases in total sleep time with sodium oxybate 9 g/night. Total NREM sleep increased with increase SWS (43.5 min) and decrease in nocturnal awakenings [155]	Federally controlled substance Schedule III drug
	Mechanism by which sodium oxybate inhibits cataplexy is unknown  Metabolized to water and carbon dioxide through Krebs cycle oxidation	Absorption is delayed by high fat meals. Half life 0.5–1 h, short half-life necessitates twice-nightly dosing	Contraindicated with concomitant sedative hypnotic agents and alcohol		FDA approved for excessive daytime sleepiness and cataplexy in narcolepsy  NOTE: sodium oxybate appears to increase growth hormone release  CAUTION: sodium oxybate associated deaths have been noted in patients with obstructive sleep apnea

For annotations, see Table 2.4 and text. MSLT Mean sleep latency test, MWT Maintenance of wakefulness. Test All drugs are pregnancy category C drugs, except sodium oxybate which is a category B drug.

ADHD attention deficit hyperactivity disorder

the perifornical area [111]. A recent study indicated that modafinil may also act by opening “gap junctions” between neurons [112].

Modafinil is a compound comprised of two enantiomers, the S-isomer with a half-life of 3–4 h and the R-isomer with a half-life of approximately 15 h. The elimination half-life is 10–12 h for single dosing and up to 15 h after multiple dosing, the maximum concentration is achieved in 2–4 h [113]. It is metabolized in the liver by the cytochrome P450 system; hence, drug–drug interactions with agents metabolized via same pathway (Table 2.8) may arise. Recommended dose is 200 mg/day but doses up to 400 mg/day, in one or two divided doses [113].

*Drug efficacy studies:* A number of reviews have analyzed data regarding modafinil efficacy in controlled trials. The reader is referred to these detailed reviews [114, 115]. A recent meta-analysis pooled data from nine randomized double-blind controlled trials [116]. The studies were double blind, placebo controlled with doses of 200–400 mg of modafinil [117–125] including 1,054 patients with narcolepsy with or without cataplexy with a length of follow-up from 2 to 9 weeks at doses of 200 mg/day [124, 125], 300 mg/day, [120] and 400 mg/day [124, 125]. Modafinil in comparison with placebo significantly decreased excessive daytime sleepiness assessed by Epworth Sleepiness Scale (ESS) with a weighted mean difference of –2.73 points (95% CI –3.39, –2.08), improved MSLT (multiple sleep latency test) and MWT (maintenance of wakefulness test) test results with a weighted mean difference of 1.11 min (95% CI 0.55, 1.66) and 2.82 min (95% CI 2.40, 3.24), respectively. There was also a decline in the duration of daytime sleepiness and the number of sleep attacks and naps per day. As expected, there was no effect on cataplexy. Following 9 weeks of treatment with 200 or 400 mg/day dosing, modafinil improved quality of life on the SF-36 questionnaire [124, 125] and also on a validated narcolepsy specific questionnaire [126]. Modafinil improved energy, attention, self-esteem, and social functioning. Performance improved in one study [120] and clinical global impression (CGI) scale of physician improved [124, 125]. The likelihood of falling asleep increased after withdrawing modafinil [122]. Modafinil had a similar effect on excessive daytime sleepiness as sodium oxybate [119] with no difference in the change in ESS scores and mean sleep latency (MSL) on MWT. Nausea was noted more often with sodium oxybate. There are no randomized controlled trials comparing modafinil with methylphenidate or other amphetamine-like stimulants. While sleepiness recurred both subjectively (ESS) and objectively (MWT) upon discontinuation of the drug, withdrawal symptoms such as those noted with amphetamines were absent, suggesting that modafinil is not “addictive” and has a lower potential for abuse [113]. Modafinil 400 mg, taken once daily or as a split dose in the morning and at midday, was significantly better at promoting wakefulness throughout the entire day than modafinil 200 mg taken once daily in the morning [127]. However, psychiatric alterations have been noted in patients under combined treatment with sodium oxybate and modafinil [128]. Patients should be monitored for psychiatric alterations in narcolepsy–cataplexy patients treated with sodium oxybate and CNS stimulant drugs.

In addition to narcolepsy, there is good evidence that modafinil is effective in reducing residual daytime sleepiness in patients with OSA despite adequate therapy

with PAP [129–131], with an improvement in quality of life. OSA patients should be told that they must continue to take their previously prescribed CPAP treatment for OSA while on the drug. Modafinil also decreased frequency and duration of lapses of attention in a clinical trial of 209 patients with SWSD who received either 200 mg of modafinil before the start of each shift [133]. There were fewer accidents or near accidents, however, there was residual sleepiness [133].

Table 2.8 provides the indications, recommended dosing, and potential adverse effects of modafinil and armodafinil. In a compilation of data from six randomized, double-blind, placebo-controlled studies, modafinil has a good safety profile [134] and is well tolerated in the treatment of excessive sleepiness narcolepsy, shift work disorder, and sleepiness related to OSA. It did not affect the sleep architecture by polysomnography or any cardiovascular parameters (blood pressure or heart rate). Polysomnography showed no notable changes in sleep architecture measures, TST, sleep efficiency, %REM sleep, latency to N1, REM latency, or arousals on polysomnography. In shift work studies, the increase in MSL objectively was small (approximately, 2 min at both 200 mg and 400 mg); however, patients' subjective assessment of sleepiness was much improved, with a reduction in the ESS score by approximately 4 points at the 200 mg dosage and 6 points at 400 mg. Clinicians' subjective assessment of overall clinical improvement was also demonstrated by CGI scales.

While modafinil is FDA approved for the three listed indications, it has been studied (off-label) in various other conditions that produce hypersomnia including traumatic brain injury [135], idiopathic hypersomnia [136], multiple sclerosis [137], and fibromyalgia as well as for alleviation of fatigue [138].

## ***Armodafinil***

Armodafinil, the R-enantiomer of modafinil, has a longer half-life of 15 h and is dosed once daily in the AM. Armodafinil has been shown to increase MSL. On 30-min MWT, armodafinil resulted in a small (2.3 min) but statistically significant increase from baseline in MSL, compared to placebo on the first four MWT sessions (0900–1500) compared with placebo in OSA patients with residual EDS. Armodafinil also reduced fatigue [139, 140]. Armodafinil also significantly increased the MWT MSL in narcoleptic patients [141]. In patients with excessive sleepiness associated with chronic SWSD, armodafinil significantly improved wakefulness during scheduled night work, raising mean nighttime sleep latency, from 2.3 (1.6) minutes at baseline to 5.3 (5.0) minutes, over a period of 12 weeks [142]. The effectiveness of armodafinil lasted after long-term use ( $\geq$ than 12 month) and well tolerated in open-label trials in patients with excessive sleepiness associated with treated OSA, SWSD, or narcolepsy [142, 143, 144]. Armodafinil was also effective in reducing sleepiness due to jet lag following eastward travel through 6 time zones [145]. The drug has been effective in the setting of fatigue related to fibromyalgia [146].

*Neither modafinil nor armodafinil is FDA approved for use in pediatric patients for any indication.* These drugs induce cytochrome P450 enzyme, leading to reduced levels of oral contraceptive. Hence, female patients should use another form of contraception while on these medications.

## ***Sodium Oxybate***

Sodium oxybate is the sodium salt of the recreational drug, gamma-hydroxybutyric acid (GHB). It is FDA approved for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy but given its abuse potential and CNS depressant effect, the drug is available only through a centralized pharmacy. Oral sodium oxybate is rapidly absorbed with a high first-pass metabolism; absorption is slowed by fatty meals, and hence, the drug should be taken a few hours after a meal [147]. Sodium oxybate is metabolized to water and carbon dioxide through Krebs cycle oxidation. It is eliminated rapidly from the circulation in 20–53 min, necessitating twice-nightly administration, taken at bedtime while in bed and again 2.5–4 h later [149].

*Drug efficacy:* While the exact mechanism of action of sodium oxybate is not known, it probably acts by binding to GHB and GABA<sub>B</sub> receptors [148]. In healthy volunteers and in patients with narcolepsy, the drug improved sleep continuity, thereby improving daytime sleepiness. There were dose-related increases in SWS duration and delta power, increases in sleep latency, and decreases in nocturnal awakenings in patients with narcolepsy with cataplexy. REM-sleep duration increased initially at lower doses, but then decreased in a dose-related manner [150]. The mechanism of the anticataplectic action is unknown. In a randomized, double-blind, placebo-controlled trial, sodium oxybate 6–9 g/night, significantly reduced the frequency of cataplexy attacks in patients with narcolepsy with cataplexy after 4 weeks of therapy, in a dose-related manner. The ESS was reduced at all doses, becoming significant at the 9-g dose ( $p=0.0001$ ). The CGI scores increased, and the frequency of sleep attacks and nighttime awakenings decreased in a dose-related fashion [151]. Additionally, a 12-month, open-label, extension trial in the same patient cohort, demonstrated that the positive benefits on cataplexy and daytime sleepiness were maintained at the end of the study period with few adverse effects. Of note, 87% of patients who entered the trial were on concomitant stimulant medications. The most common adverse events were headache, nausea, viral infection, dizziness, pain, enuresis, and somnolence [151, 152]. There was a significant median increase of >10 min in the MWT after therapy with 9 g of sodium oxybate in adults with narcolepsy with cataplexy.

Nightly doses of 4.5, 6, and 9 g sodium oxybate for 8 weeks resulted in statistically significant median decreases in weekly cataplexy attacks of 57.0, 65.0, and 84.7%, respectively [153]. Sodium oxybate as monotherapy or in addition to the stimulant modafinil induced 5 or 26% increases in mean sleep onset latency on MWT. Sodium oxybate and modafinil produced additive effects when used together for the

treatment of excessive daytime sleepiness in narcolepsy [119]. After 8 weeks, significant changes in sleep architecture among patients receiving sodium oxybate and sodium oxybate/modafinil included a median increase in Stage 3 and 4 sleep (43.5 and 24.25 min, respectively) and delta power and a median decrease in nocturnal awakenings (6.0 and 9.5, respectively) [155]. There was a significant improvement in the functional status measure of quality of life using the Functional Outcomes of Sleep Questionnaire [156].

*Side effects:* Sodium oxybate was well tolerated and the most common adverse events were headache, dizziness, nausea, vomiting, pain, enuresis, somnolence, and nasopharyngitis [152]. Sleepwalking was reported in 4% of 717 patients treated in clinical trials with sodium oxybate [153]. Although not systematically evaluated in controlled clinical trials, no acute withdrawal symptoms were observed after 2 weeks of discontinuation following an average of 21 months of therapy (range: 7–44 months). The abrupt cessation of sodium oxybate therapy resulted in a significant increase in the number of cataplexy attacks, however, the cataplexy attacks returned gradually and there was no acute rebound in cataplexy [157].

Sodium oxybate is a Schedule III drug. GHB (parent drug) abuse at high doses has been associated with CNS depression, bradycardia, hypotension, seizure, respiratory depression, depressed level of consciousness, with instances of coma and death [158]. Thus, strict risk-management strategies and rigorous adherence to the up-titration schedule are needed. Synergistic interactions of GHB with alcohol or other CNW depressants may increase the risk of intoxication or overdose. There is limited information about efficacy and safety in elderly populations and in patients less than 16 years of age. Daily sodium intake should be considered in patients with heart failure, hypertension, or compromised renal function. Patients with compromised liver function should have their starting dose decreased by one half and response to dose increments monitored closely [148, 185].

## Drugs of Abuse

Effects of illicit drugs on sleep can be studied under two main headings, effects on sleep after acute or chronic exposure and effects on sleep after withdrawal or discontinuation of the drug. Alcohol is commonly self-administered as a sedative to treat sleep-onset insomnia. It is sedating via binding to the GABA receptor. In 17 young male adults, a single acute dose of alcohol prior to bedtime produced a significant decrease in percent stage REM during the first half of the night, with a reduction in the average length of the first REM episode from 18.6 min during baseline to 12.1 min on the alcohol night ( $p < 0.05$ ) [159]. During the second half of the alcohol night, there was a significant “rebound” increase in REM sleep with a concomitant reduction in stage 2 sleep. Thus, alcohol apparently affected the distribution of REM sleep. Alcohol did not cause a significant alteration in the total amount of REM sleep in this study [159]. Table 2.9 lists the mechanisms of action of alcohol and illicit drugs of use and their effects on sleep [159–171].

**Table 2.9** Drugs of abuse and their effects on sleep

Drug	Site of action	Effect of drug administration	Effect of drug withdrawal/abstinence
Alcohol [159]	GABA receptor agonist	<i>First portion of the night:</i> acute effect of alcohol decreases REM% with reduction in average length of the first REM episode	<i>Second portion of the night:</i> after alcohol is metabolized, there is significant “rebound” in REM sleep with reduction in stage 2 sleep. REM sleep behavior disorder may appear following chronic alcohol use.
Cocaine [161]	Inhibition of presynaptic dopamine transporters, increased dopamine availability	PSG: longer sleep latency, reduced total sleep time, and suppression of REM sleep after acute drug administration	Significantly reduced TST, SE, prolonged SOL, increased REM percentage, and reduced REM latency (increased dreaming) followed by insomnia and REM disturbance.
3,4-methylenedioxy methamphetamine (MDMA) [162] (Ecstasy)	Rapid release of serotonin, binds to serotonin 5-HT2 receptors, rapid dopamine release	Animal studies show increased wakefulness after acute use, associated with circadian clock abnormalities [160]	Persistent effect of MDMA after abstinence: there was reduced stage 2, TST, increased stage 1, reduced REM latency, REM suppression, possible increased sleep efficiency and SWS [163, 164].
Cannabis (Δ-9-tetrahydrocannabinol is the active compound) [160]	Cannabinoid CB1-receptors [160]	THC increases wakefulness and decreases total REM sleep and REM density, variable effect on SWS, but may increase REM sleep in chronic users [165–168]	Sleep difficulty and strange dreams are frequently reported effects of marijuana withdrawal with increased sleep onset latency and wakefulness after sleep. There is reduced SWS and increased REM sleep [165–167].
Opiates [170, 171]	Opioid receptors 12	Dose related decreased in TST, SWS and REM sleep. Increased arousals and wakefulness after sleep onset [169] in some studies no change in SWS. Chronic use is associated with central apneas with ataxic breathing [170, 171]	Withdrawal after chronic opioid use is associated with initial insomnia and decreased REM; during protracted abstinence phase, TST significantly increases with rebound SWS and REM sleep between 13 and 22 weeks following withdrawal of opioids [171]

For annotations, see Table 2.4



## New Drugs Under Development

Several agents, both stimulants and sedatives, are in development for the treatment of sleep disorders. Potential sedating drugs in development include tiagabine, partial GABA agonists, new M1–M2 agonists, and other selective serotonin subtype receptor antagonists (5HT2A). Drugs that antagonize the activating histaminergic system are also sedating [172–174]. There is also great interest and potential for developing novel wake-promoting drugs, such as hypocretin agonists and other hypocretin-based therapy. However, a major limitation is that hypocretin-1 does not cross the blood–brain barrier and, therefore, cannot reach the CNS [175]. Thyrotropin-releasing hormone (TRH) agonists increase alertness and are wake promoting as well as anti-cataplectic in the narcoleptic canine model [176]. These can be developed as potential drugs for narcolepsy. Additionally, further studies investigating the role and efficacy of almorexant, agomelatine, and histamine antagonists will allow us to add these to our armamentarium of drugs that treat sleep disorders.

## Summary of Keypoints

- Sleep- and wake-promoting drugs act by modulation of key sleep- and wake-promoting neurotransmitters and their corresponding receptors sites.
- GABA ( $\gamma$ (gamma)-amino butyric acid) is an important sleep-promoting neurotransmitter. Potentiation of GABA activity produces sedation. Benzodiazepines and NBRAs promote sleep by binding to the GABA<sub>A</sub> receptor and modulating the flow of chloride ions into the cell, thereby inhibiting neuronal activity. Depending on the half-life, these drugs improve sleep latency, sleep maintenance, total sleep time, and overall sleep quality. Unlike the benzodiazepines, the NBRAs do not alter the REM or SWS percentages.
- Ramelteon and tasimelteon reduce sleep latency by binding selectively to the MT1 and MT2 receptors in the SCN, without producing changes in REM or SWS.
- One needs to be aware of the potential side effects, contraindications, and drug interactions of these agents. Sedatives can potentially have a “hang-over effect” the next day and may be associated with complex behaviors during sleep.
- A number of antidepressants and antipsychotics have been used “off-label” as sedatives. Low dose doxepin is now FDA approved as the first antidepressant with an indication for the treatment of sleep maintenance insomnia. The high specificity and affinity of doxepin to the histamine H(1) receptor allows it to be a good sedative at low doses without concomitant major anticholinergic side effects.
- Almorexant and other orexin/hypocretin antagonists are novel drug types under development and undergoing phase II and III clinical trials in patients with insomnia.
- Amphetamine-like stimulants, as well as modafinil and armodafinil are wake promoters that act via activation of the noradrenergic, dopaminergic, serotonergic, and/or histaminergic systems. These drugs are prescribed for patients with narcolepsy.

- Modafinil and armodafinil are also FDA approved for reducing residual daytime sleepiness in patients with OSA despite adequate therapy with PAP and for patients with SWSD.
- Sodium oxybate increases SWS, reduces nocturnal awakenings, and promotes wakefulness probably via activity at the GABA<sub>B</sub> or GHB receptor sites. It is approved for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy but given its abuse potential and CNS depressant effect, the drug is available only through a centralized pharmacy. Strict risk-management strategies and rigorous adherence to the up-titration schedule are recommended.
- Several agents, both stimulants and sedatives, are in development for the treatment of sleep disorders. These include partial GABA agonists, new M1–M2 agonists, histamine antagonists, other selective serotonin subtype receptor antagonists (5HT<sub>2A</sub>), hypocretin receptor antagonists, among others.

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# Chapter 3

## Obstructive Sleep Apnea: Diagnosis with Polysomnography and Portable Monitors

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**Keywords** Sleep • Apnea • Diagnosis • Lung • Monitoring • Breathing

### Introduction

Definition of Obstructive Sleep Apnea (OSA): OSA is the leading cause of referral to sleep laboratories worldwide, accounting for at least 75–80% of diagnoses [1, 2]. In the last few decades, there have been considerable advances in knowledge regarding the underlying mechanisms, diagnostic approaches, treatment options, and the impact of OSA on personal as well as public health of OSA since the disease terminology was first coined. The current definitions of sleep apnea are not uniform, but most of them attempt to characterize the frequency of sleep-disordered breathing events (e.g., AHI “Apnea–Hypopnea Index” or RDI “Respiratory Disturbance Index”) along with the severity (e.g., oxygen desaturation) of each event (e.g., complete (apnea) and partial (hypopnea) cessation of breathing during sleep) [2]. By convention, an apnea is defined as greater than 90% reduction of air flow for at least 10 s [2–5]. A hypopnea is defined as a reduction in airflow that is followed by an arousal from sleep or a decrease in oxyhemoglobin saturation. While AHI is the most commonly used parameter to assess sleep apnea severity, several additional measures of sleep such as the degree of nocturnal oxyhemoglobin desaturation and the amount of carbon dioxide exhaled have been used to characterize disease severity in clinical and research settings [6, 7].

The mechanisms of sleep-disordered breathing are complex, but can involve either obstruction of the upper airways (OSA) in the presence of intact respiratory

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drive; the absence of ventilatory drive (CSA or central sleep apnea) in the presence of a patent airway; or mixed apnea, which has features of both OSA and CSA [8]. Pure CSA is much less common than OSA in the general population; CSA occurs most often in individuals with congestive heart failure (CHF) or occasionally with neurological compromise or chronic narcotic intake.

Patients with OSA can frequently experience sleep fragmentation, daytime somnolence, or suboptimal psychomotor function. Untreated OSA can also lead to common comorbidities such as hypertension, diabetes, stroke, and depression. Individuals with moderate and severe OSA have increased risks for hypertension, cerebrovascular accident (CVA), cardiovascular diseases, diabetes mellitus, depression, road traffic crashes, poor performance in school and work, and decreased productivity in the workplace [9–15].

## Prevalence and Epidemiology

The estimated prevalence of symptomatic OSA in the United States in early 1990s by Young et al. was 4% among adult men and 2% among adult women [16]. Since then, prevalence data from other countries have emerged. The prevalence of OSA associated with daytime sleepiness is 3–7% in adult men and 2–5% in adult women [2, 17]. Subgroups of those populations have higher prevalence, including persons with older age, male gender, and obesity. Though diagnostic methodologies vary, most available epidemiologic data on prevalence of OSA confirm Young's finding across the globe [16, 18–22]. Interestingly, the prevalence of OSA in developing countries such as India and China is on the same order of magnitude as that in the developed countries, despite less obesity. Therefore, OSA is not only a disease of more developed countries, but a common disease worldwide. Additionally, there are huge and growing individual and public health costs associated with OSA, whether from lost productivity at work places, motor vehicle accidents from drowsy driving, or the cardiovascular and metabolic comorbidities of OSA. Because the obesity epidemic is spreading worldwide, we can only imagine an increasingly higher prevalence of OSA in the twenty-first century [23].

## Risk Factor

Despite substantial research on OSA in the past several decades, OSA remains underdiagnosed [24]. This is due in part by the lack of awareness of the disease by patients as well as the general public, and insufficient clinical suspicion on the part of physicians. Therefore, it is important for clinicians to gain proper knowledge of OSA risk factors, so that timely diagnoses can be made and treatment can be initiated.

OSA risk factors include obesity, older age, male gender, postmenopausal status, Asian/African American races, tobacco, and alcohol use [5, 25]. Studies have shown

that up to 70% of men and 56% of women between age 65 and 99 year have some form of OSA [26]. The mechanisms for age-related OSA include deposition of adipose tissue in the parapharyngeal area and anatomical changes surrounding the pharynx [27, 28]. Disease prevalence for OSA is relatively low among premenopausal women and increases postmenopausally [29]. Obesity is the single most treatable factor predictive of OSA. Data collected in Sleep Heart Health Study (SHHS) have shown that moderate and severe OSA is independently associated with BMI, neck circumference, as well as waist circumference. Individuals with OSA have significantly more visceral distribution of fat than central fat after controlling for BMI. Visceral fat is significantly correlated with AHI [30]. Waist-hip ratio has also been shown in some studies to be more predictive of severe OSA than obesity in general [31]. Only 10–15% of the population with diagnosis of OSA have body mass index (BMI) less than 25 kg/m<sup>2</sup> [32]. Individuals with large neck circumferences (men >17 in., women >16 in.) should raise the clinician's suspicion for OSA.

There are multiple theories as to why OSA prevalence in women is lower than that in men. One of them is that male bed partners of women are less likely to report bedtime symptoms of OSA than the female bed partners of men. Women with OSA also tend to have less “classic” daytime symptoms of OSA; instead of reporting daytime sleepiness they may report fatigue and lack of energy. Lastly, women have different anatomical and functional properties of their upper airways and differences in control of breathing. Thus, both diagnostic biases and biological factors contribute to the gender imbalance in sleep apnea prevalence.

Among different races, obesity plays a varying degree of importance. Middle-aged (age 25–65 years) African Americans have similar disease prevalence than the other racial groups, but adult African Americans younger than 25 years or older than 65 years have a higher prevalence than the others [29, 33]. Among the East Asian population, though the prevalence of obesity is less than the whites, the prevalence of OSA is not less than that in the West. Therefore, the relationship between obesity and OSA is less clear-cut among Asians. However, differences in adipose tissue distribution (i.e., peripheral vs. visceral) may play a more significant role in Asians [34]. Additionally, craniofacial profiles such as crowded posterior oropharynx, shorter cranial base, and more acute cranial base flexure also seem to be important in pathogenesis of OSA among nonobese populations [35, 36].

## Clinical History

A sleep history looking for OSA should be obtained either as a routine health maintenance evaluation, part of an evaluation for potential OSA in a symptomatic person, a comprehensive evaluation of those at high risk for OSA, and as a part of a screen for sleep disorders in commercial drivers, other transportation operators and persons involved in safety-sensitive work. A good sleep history should address both sleep and wakefulness. Because individuals with OSA often disrupt their bed partners' sleep, bed partners should be encouraged to participate in this part of the evaluation process.

**Table 3.1** Five questions to screen patients for obstructive sleep apnea (OSA)

Question 1	“Do you have trouble falling asleep or maintaining asleep at night?”
Question 2	“Have you ever been told that you snore during sleep?”
Question 3	“Have you ever woken up choking or gasping for air when you are asleep?”
Question 4	“Has anyone ever witnessed you stop breathing during sleep?”
Question 5	“Do you have trouble staying awake during the day?” (Epworth sleepiness score questionnaire)

Loud snoring, awakenings due to choking and/or gasping, and witnessed apneic episodes during sleep are common symptoms reported by OSA patients or their bed partners [37, 38]. OSA can make falling asleep and maintaining sleep difficult [39]. Excessive daytime sleepiness (EDS) is a common complaint, although many patients do not report sleepiness per se. For an individual with OSA, EDS most likely will persist even after adequate amount of total sleep time (TST) is achieved. The Epworth Sleepiness Scale (ESS), a self-reported score combining a series of answers for likelihood of dozing off in eight different scenarios [40]. An ESS of greater than 12 (out of 24) is usually considered “sleepy.” Though subjective, ESS is frequently used to quantify EDS and is useful as a reference scale for assessing future treatment effectiveness. Questions on general sleep history such as TST, sleep fragmentation, sleep maintenance, as well as questions related to insomnia (difficulty falling asleep or going back to sleep) should also be asked to generate a differential diagnosis. Lack of concentration and/or cognitive abilities, decreased libido, risk of motor vehicle accidents, mood disorders, morning headaches, and dry mouth are other common complaints in OSA patients. History of common comorbidities such as hypertension, stroke, myocardial infarction, cor pulmonale, and arrhythmia should also be obtained. In pediatric populations, the complaint of excessive sleepiness is often replaced by hyperactivity, attention deficit, and mouth breathing. OSA is more frequently present among children of OSA subjects, suggesting the role of genetic factors in OSA. Table 3.1 lists questions that a healthcare provider should ask of an individual suspected of having OSA.

Taking a medical history from certain populations among whom symptoms and signs of OSA may affect their employment status may be challenging. For example, unlike the sleep clinic setting where patients are seeking diagnosis and treatment for sleep difficulties, it is common for commercial vehicle drivers, pilots, and train operators to avoid an OSA diagnosis because of its economic and occupational implications. Thus, relying on self-reported symptoms by commercial drivers for screening for OSA has a very low yield in these occupational settings [41–44]. These groups often do not report any symptoms [42, 44]. Furthermore, drivers with previously diagnosed OSA initially have been reported to deny the presence of a sleep disorder until they are told that based on screening criteria they are required to obtain a sleep study. A 2006 study in Israel showed 78% of its commercial drivers

**Table 3.2** Common risk factors of obstructive sleep apnea (OSA)

Anthropometric measures	BMI >28 kg/m <sup>2</sup> , neck circumference >17 in. (43 cm) for men, or >16 in.(41 cm) for women
Physical exam	Retrognathia, high modified mallampati score (III/IV), large tonsils (>2), macroglossia
Age	Age 35 or greater
Ethnicity	Asian, African American, Hispanic ethnicities
Gender	Male gender
Hormone	Postmenopausal status in women
Habits	Alcohol, tobacco

with BMI greater or equal to 32 kg/m<sup>2</sup> had polysomnography (PSG)-confirmed OSA and almost half had objectively confirmed EDS as measured by a multiple sleep latency test (MSLT), but 100% of the affected drivers denied symptoms of OSA or EDS [41]. Likewise, most OSA-affected commercial motor vehicle (CMV) operators report very low ESS score at driver certifications exams (range 3–4 or 2–5 out of 24), which are markedly lower than average ESS scores among college and medical students (range 7–8) [40–42]. Therefore, at the present time, examiners must rely primarily upon anthropometric and other objective criteria when evaluating transportation operators.

A summary statement from the Joint Task Force (JTF) of American College of Occupational and Environmental Medicine/American College of Chest Physicians/ National Sleep Foundation of screening criteria for OSA among CMV operators was published in the journal *Chest* in 2006 [45]. The statement recommends a 3-month maximum certification, pending OSA evaluation, for the CMV operator if the operator falls into any one of the five major categories. Of note, the only objectively measurable major category in the JTF statement is the subject’s anthropometric characteristics and blood pressure measured during the office visit. Therefore, in the setting of occupational certification, the suspicion for OSA should be elevated with or without a clear subjective reporting of symptoms of OSA (i.e., EDS). Timely referral for an OSA evaluation is warranted, if the examinee seeking certification has two of the following three objectives measurements in clinic:

1. BMI >35 kg/m<sup>2</sup>
2. Neck circumference >17 in. in men or 16>in. in women
3. Hypertension

Patients with first-degree relatives with OSA are more likely to have OSA than those without first-degree relatives with OSA. Additionally, multiple medical conditions have been associated with OSA. In the field of endocrine disorders, type 2 diabetes, polycystic ovary syndrome (PCOS), and hypothyroidism are known to be associated with OSA. Congenital diseases such as Down’s syndrome or microcephaly are associated with OSA [46]. Pregnant women can present with OSA as gestational weight gain progresses. Occasionally, rare anatomical abnormalities of the airway such as Eagle Syndrome can cause OSA. Table 3.2 illustrates common risk factors for OSA.



## Physical Exam

Vital signs can frequently reveal hypertension in people with OSA. Neck circumference should be documented as it is an important anthropometric measurement. Obesity (BMI of  $\geq 30$  kg/m<sup>2</sup>) is probably the most common finding among OSA patients. The rest of the physical exam should include head and neck, airway or respiratory, cardiac, neurologic exams. The head and neck exam of an OSA patient can present with crowded posterior pharyngeal space (i.e., modified Mallampati III or IV), large tongue with teeth mark (macroglossia), tonsillar hypertrophy, dental malocclusion (class II), retracted mandible relative to the maxilla (retrognathism or micrognathism), or deviated nasal septum. In children with OSA, hypertrophied adenoids or tonsils are common, and children often compensate by becoming obligatory mouth breathers [46]. Nasopharyngeal fiber scope can be used in office to evaluate for the shape and size of the retropalatal/retroglossal airway, though there is no currently available evidence-based guidelines using this as a diagnostic tool. Internal jugular venous distension and peripheral edema should be assessed as part of the heart exam. Cardiac auscultation and pulse palpation can be helpful, particularly given the known association between atrial fibrillation and sleep apnea. Neurological examination should focus on muscle strength and presence of any focal deficits, since neuromuscular disease can present with sleep apnea and/or hypoventilation.

## Diagnosis of OSA

There are currently two major methods to diagnose OSA: full in-lab PSG and portable monitoring (PM) or Limited-Channel Testing (LCT) device. There is much ongoing debate as to the utility of each diagnostic tool. In general, PSG offers more thorough measurements of various aspects of sleep, but it is time consuming, expensive, and performed outside the home. PM offers convenience to patients, but PM is limited by its reduced sensitivity, specificity, and measured information. Patient history and physical exam are key determinants for diagnostic route. Due to financial considerations, PM is becoming increasingly common in the USA and has been used with reasonable success worldwide. There are four types of PMs Type I–IV, in the order of decreasing measurements of sleep and respiratory variables (see Table 3.3).

### *Overnight Polysomnography (PSG)*

The current gold standard test for assessing the severity of OSA is in-laboratory, technician-monitored PSG. A Full PSG (or type I monitor) has been performed since the 1960s [47]. The initial uses of PSG were to assess sleep physiology in normal individuals and those with various neurologic or sleep disorders such as



**Table 3.3** Summary characteristics of polysomnogram (type I) and portable monitor (type II–IV)

	Type I PSG	Type II PSG	Type III PSG	Type IV PSG
Monitoring personnel	Yes	No	No	No
Oximetry	Yes	Yes	Yes	Yes
Respiratory effort	Yes	Yes	Yes	No
Air flow	Yes	Yes	Yes	No
Body positions	Yes	Yes/No	Yes/No	No
EMG-AT	Yes	Yes	No	No
EEG	Yes	Yes	No	No
ECG-heart rate	Yes	Yes	Yes	No
EOG	Yes	Yes	No	No
Surface EMG	Yes	Yes	No	No
Video recording	Yes/No	No	No	No
Sound recording	Yes/No	No	No	No
Minimum number of channels for CMS* reimbursement	14–16	≥7	≥4	≥3

seizures, insomnia, narcolepsy, periodic limb movement, and the parasomnias, as well as to examine the effect of hypnotics and other drugs on sleep. The pulmonary components of the PSG were added later as OSA was becoming increasingly appreciated in the 1970s.

PSG, which is usually performed as an overnight study, typically assesses physiological parameters by recording sleep–wake stage, heart rhythm, skeletal muscle activities, respiratory patterns, sound of snoring, and oxygen saturation. Each of the above respective components is monitored by electroencephalogram (EEG), electro-oculogram (EOG) or eye movement, heart rate and rhythm (ECG), electromyogram (EMG) of skeletal muscle activity (usually at the chin and tibialis anterior), respiratory effort, snoring (microphone), respiratory air flow, thermistor, and pulse oximetry. Nasal pressure technology is also commonly used to detect subtle respiratory events since it has been shown to be more sensitive than standard thermistor. However, the specificity of nasal pressure has been less well studied, i.e., the consequences of these subtle events (which are not observed in the thermistor) are unclear [48–51]. Occasionally, sleep studies are done at different times of the day, depending on the suspected symptoms of the subjects (circadian rhythm disorder, etc.).

The definition of OSA currently involves the measured AHI, the average number of apnea and hypopnea episodes over an hour. RDI has also been used as an alternative scale for those measures. We can think of AHI as a subset of RDI, as the definition of RDI is less strict than AHI. During a full overnight PSG, an apnea is defined by AASM as cessation (more than 90% reduction) of air movement lasting 10 or more seconds [3]. As stated previously, the distinction between RDI and AHI is related to “respiratory effort related arousals” (RERA), which are subtle hypopneas. These RERAs are included in RDI but not in AHI. Apnea can be distinguished from hypopnea via a thermistor in PSGs, although the consequences of hypopneas vs. apneas are generally felt to be similar. While the definition of apnea has been less debated, the definition of hypopnea is far from settled [3]. The ideal hypopnea definition is unknown.

**Table 3.4** Commonly used PSG criteria for scoring hypopnea [3]

Criteria names	Definitions of hypopnea (at least one of the followings)
“Chicago criteria”	Reduction of airflow $\geq 50\%$ Reduction of airflow $< 50\%$ and oxyhemoglobin desaturation $> 3\%$ Reduction of airflow $< 50\%$ and EEG evidence of arousal
AASM recommended or “medicare criteria”	Reduction of nasal pressure $\geq 30\%$ Oxyhemoglobin desaturation $\geq 4\%$
AASM alternative	Reduction of nasal pressure $\geq 50\%$ and oxyhemoglobin desaturation $\geq 3\%$ Reduction of nasal pressure signal $\geq 50\%$ and EEG evidence of arousal

There are historically at least three different criteria to score hypopneas: the AASM recommended criteria, and AASM alternative criteria and the “Chicago Criteria” (see Table 3.4).

The “Chicago Criteria” was the 1999 version of the AASM recommended criteria for hypopnea. These criteria were designed mainly for clinical research rather than clinical practice. The Chicago Criteria defines hypopnea as having one of the following three features:

1. Reduction of airflow (by thermistor)  $\geq 50\%$
2. Reduction of airflow (by thermistor)  $< 50\%$  and oxyhemoglobin desaturation  $> 3\%$
3. Reduction of airflow (by thermistor)  $< 50\%$  and EEG evidence of arousal

Nasal pressure was early in development at the time of Chicago criteria and was suggested but not strongly recommended. The lack of hypopnea criteria for clinical practice was further addressed by AASM in 2001. Via the Clinical Practices Review Committee, AASM defined hypopnea as having at least 30% reduction of airflow lasting at least 10 s, and with 4% reduction in oxyhemoglobin saturation. Since then, the 2001 AASM definition has been adopted by Center for Medicare and Medicaid Services (CMS) as its criteria for AHI scoring. However, the 2007 Manual for Scoring of Sleep and Associated Events published by AASM introduced only two definitions: “recommended” and “alternative” [3]. The AASM Recommended Criteria is the same as the desaturation-based Medicare criteria, i.e., with no importance placed on arousal from sleep:

1. Reduction of nasal pressure signal  $\geq 30\%$  and oxygen desaturation  $\geq 4\%$

The Alternative Criteria by AASM defines hypopnea as one of the following two features:

1. Reduction of nasal pressure signal  $\geq 50\%$  and oxygen desaturation  $\geq 3\%$
2. Reduction of nasal pressure signal  $\geq 50\%$  and associated arousal

A common obstacle in communications between sleep specialists and primary care physicians (PCPs) is that sleep reports often do not specify which criteria the

sleep lab has adopted as a standard for scoring OSA [52, 53]. The same obstacle is magnified further in the case of diagnostic interpretation of OSA using PMs. Therefore, any sleep report should include not only the calculated AHI or RDI, but also an explanation of the criteria used for scoring.

The severity of sleep apnea is typically assessed by AHI, but AHI correlates only loosely with EDS and other outcomes [14, 54]. Different parameters measured by a sleep study are predictive of various outcomes of OSA [55]. For example, the degree of oxyhemoglobin desaturation threshold may vary depending on the clinical or research outcome of interests (i.e., hypertension vs. insulin resistance vs. memory consolidation). Additional markers have been suggested as risk factors for disease severity; for example, the degree of nocturnal hypoxemia and the frequency of arousal from sleep. Therefore, when discussing sleep study findings, it is imperative for clinicians to integrate patient's initial chief complaint, unique history, risk factor, and life style into the assessment. In addition, further data are required regarding which disease indices have the best predictive value for various outcome measures.

The limitations of in-lab PSG include the "first-night" effect where sleep is less than usual due to being in a foreign environment, night-to-night variability of the findings, effects of sleep position (which may be different in home, with a bed partner), and the effects of certain medications (i.e., selective serotonin receptor inhibitors, benzodiazepines, hypnotics/alcohol, and stimulants). In-house PSG is quite labor intensive, requiring oversight by a skilled sleep technician. However, in-lab PSG remains the gold standard for diagnosis of OSA given the reliability and quantity of the data provided.

### ***Split Night Study (Diagnosis Combined with Titration)***

Frequently a "split-night" study can be done during a full in-laboratory PSG. In a "split-night" study, an initial impression of the severity of OSA undergoes a "real-time" assessment by a supervising technician. If the patient qualifies for moderate or severe OSA during the first half of the overnight study, a titration study is initiated in the second half of the night to determine an appropriate positive airway pressure (PAP) for treatment. A split-night study is theoretically less sensitive than a full nocturnal study because the AHI is assessed in half of the usual duration. A recent study, however, showed that the AHI derived from the first 2 or 3 h of a split-night study is of sufficient diagnostic accuracy to rule-in OSA at an AHI threshold of five in patients suspected of having OSA [56]. However, medical history is important in interpretation of the split-night study. For example, patient's underlying unusual circadian rhythm as well as sleep-onset/sleep-maintenance insomnia can alter the diagnostic impression of the study. All things considered, the need to extend the "split-night" study into a second nocturnal study is uncommon. Therefore, a "split-night" study not only brings convenience to the patient by avoiding an extra evening of titration study but also reduces the overall cost for the diagnosis and treatment of OSA. A split-night study has become the "default" study type for individuals suspected of OSA.

## ***Portable Monitoring (PM)***

PM, or LCTs, is a simple methodology to diagnose OSA. PM testing gives limited data (discussed in detail below) but perhaps is more comfortable for the subject and thus offers a more natural perspective for the severity of OSA at home. However, without a technician on site, the quality of PM studies is only as good as the technologies available.

### **Types of PMs (Type II–IV)**

The American Academy of Sleep Medicine (AASM) has classified sleep studies into four types, depending on the channels they record and evaluate [57]. Type I PSG serves as a reference standard PSG, and it is usually a nocturnal, technician-attended, full in-laboratory sleep study with 14–16 channel monitoring. Type II–IV sleep studies are all simplified versions of Type I PSG [58, 59]. Type II records essentially the same information as full in-lab PSG, except that technician attendance is not present. SHHS, a large NIH-funded multiyear multicentered cohort study on the cardiovascular and other consequences of sleep-disordered breathing, used Type II portable monitors for diagnosis of OSA at home [60].

Type III PM has been the focus of an ongoing debate on the effectiveness and utility of PMs in diagnosing OSA. Type III PM includes oximetry, at least two respiratory channels (two airflow channels or one air flow plus one respiratory effort channel) and ECG-monitored heart rate, but it does not include EEG, EMG, and EOG. As a result, signals used to detect sleep stages and arousals from sleep (seen in Type I and II sleep studies) are missing in Type III PM. Therefore, Type III PM cannot calculate a true AHI, RDI, or sleep efficiency as it does not record the denominator, sleep time. Instead, Type III PM can only report a value defined by respiratory events divided by total recording time. However, the value reported by Type III PMs does not necessarily imply sleep was recorded. Given that not all study time is necessarily sleep time, reporting from Type III PM is a less sensitive method than values from Type I or II PSG. Another major problem for Type III PM is that without documenting sleep, an individual could wear the device (or give it to someone else) and stay awake yielding an artifactually low AHI. It is worthwhile to mention that “AHIs” or “RDIs” reported by different Type III PMs also vary with different device manufacturers. Therefore, exact definitions of “AHI” or “RDI” vary across different studies of Type III PMs.

The inability to detect respiratory event-related arousals (RERAs) may lead to underestimation of the RDI and underrecognition of upper airway resistance syndrome (UARS). Positional OSA can also be underdiagnosed by those Type III PMs that do not include body position. Naturally, a “split-night” study is not applicable for individuals who undergo Type III PM. A separate overnight in lab titration study will likely be necessary for CPAP set up should the individual be diagnosed of OSA by a Type III PM device.

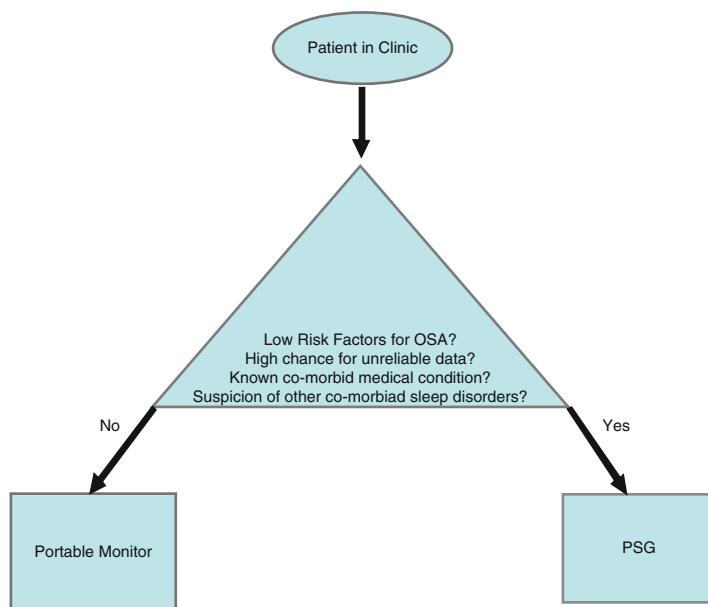
Pulse oximetry and airflow are the physiological variables that are most commonly measured in Type IV PM. As a result, the frequency of apneas or hypopneas (AHI) as well as the baseline, mean, frequency, duration, and degree of oxyhemoglobin desaturation can be estimated. Naturally, Type IV PMs share at least the same shortcomings of Type III PM, and the current CMS requires a minimum of three channels to meet the reimbursement criteria. However, we emphasize the sensitivity and specificity of the various diagnostic techniques rather than the number of channels per se.

### **When Should PM Be Considered for Diagnosis of OSA?**

While PM has an obvious advantage over PSG in its ease of use, the safety, reliability, and diagnostic accuracy of PMs have been controversial [58]. Bodily injuries from loose wires, faulty oximeter, and monitor disconnection by PMs have been reported. Data loss in Type III and IV PMs have been estimated to be between 2 and 18%. Additionally, interrater and intrarater reliability as well as night-to-night variability of PM is greater than those of PSG. Currently, the scoring of apnea and hypopnea events can be done either manually by a technologist or sleep physician, automatically by the software of the PMs, or combined (manual correction on the automated scoring is allowed). However, subtle points such as positional severity of OSA are more difficult to characterize unattended PM than PSG. The lack of standardization of testing and scoring protocols for PM is of greater concern as there are greater differences in signals recorded by different PM devices. In a comprehensive literature review done by AASM, false negative results in unattended PM studies could be as high as 15–17%. Likewise, false positive results in unattended home PM studies could be as high as 30% [61].

The American Academy of Sleep Medicine published its first guidelines for usage of PM in the diagnosis and management of patients with OSA in 2007 [57]. The guidelines stated the following principles for clinicians who consider PM as an alternative to PSG. PM usage should only be considered as part of an integrative patient evaluation for OSA, under the direction of a sleep specialist board certified in sleep medicine.

The one-size-fit-all approach to screen for OSA in the general asymptomatic population is not only medically and ethically unsound but also expensive and inaccurate in terms of healthcare cost and clinical outcome. Whether an individual should undergo PM vs. PSG depends on the individual's OSA risk factors, physical exam, medical comorbidities, suspicion of non-OSA sleep disorders, suspicion of any secondary gain/loss from the test result, and an overall pretest probability for OSA. PM should only be used for screening in subpopulations in which there is substantial published knowledge on specificity and sensitivity of the test. PM can be considered an alternative to PSG for patients with high pretest probability for moderate to severe OSA. Furthermore, PM is not appropriate for diagnosis of OSA in patients with major comorbid medical conditions that would lower the accuracy of PM (i.e., severe pulmonary disease, neuromuscular disease, CHF, CSA). PM should not be used for the diagnostic evaluation of OSA in patients suspected of having



**Fig. 3.1** Portable monitor vs. in-lab PSG decision-making diagram

other sleep disorders such as CSA, periodic limb movement disorder (PLMD), insomnia, parasomnias, circadian rhythm disorders, or narcolepsy. The utility and efficacy of Type III PM have not been adequately studied for use in the occupational setting in diagnosing at risk operators of motor vehicle operators, who, unlikely the general population, often avoid an OSA diagnosis. Figure 3.1 illustrates the decision-making diagram clinicians can use to decide if PSG or PM should be used to diagnose OSA in a patient.

The United States CMS in 2008 approved reimbursement for the uses of PMs, after Agency for Health Quality Research (AHQR) published a mostly positive review of the PMs, particularly pertaining to its comparable clinical utility to predict clinical outcomes (i.e., CPAP compliance rate) in a population with high pretest probability [59, 62–64].

### ***Current Roles of Autotitrating Positive Airway Pressure (APAP)***

Autotitrating positive airway pressure (APAP) devices have been increasingly used for titrating pressure and treating adult patients with OSA in the last decade [59, 65–68]. The devices can be used in place of in-lab continuous positive airway pressure (CPAP) titration study when attended CPAP titration is not possible or patient comfort is a great concern. They work by changing the treatment pressure based on patients' airflow, pressure fluctuations, or airway resistance.

As PMs are increasingly used as an initial diagnostic tool in populations with high likelihood of moderate to severe OSA, APAP has been identified as a partner strategy in the treatment phase to replace the more costly CPAP titration with in-lab PSG. We note here that the 2008 AASM Guidelines for APAP stated that APAP devices can only be used for unattended treatment of patients with moderate and severe OSA without significant comorbidities such as CHF, COPD, and CSA [61]. Since then, a large VA study by Berry et al. demonstrated that diagnoses by PM followed by APAP titration resulted in comparable CPAP adherence and clinical outcomes to using traditional in-lab PSG [69]. However, as APAP technology is fast evolving, different APAP devices differ not only in their sensitivities to detect severity of disordered breathing but also in their responses to disordered breathing. Therefore, overall assessment of cost-effectiveness of APAP combining with PMs is complicated.

### ***Cost Effectiveness of PSG vs. PM***

Although the cost of PM devices has seen a substantial drop in recent years, the total health care cost of evaluating and treating individuals with OSA using PM compared to PSG has not been studied adequately and largely controversial. Though gross cost savings were frequently reported, the high false negative rate of PMs along with the current guideline that all negative tests of PMs should be referred to a full in-lab PSG by a sleep specialist translates into high cost if the currently available PMs were to become the mainstream of screening tools. Furthermore, few cost analyses compared usage of PMs to increasingly popular use of split-night study protocols, in which both diagnostic PSG and titration studies are done in a single night. Further studies using a decision model are much needed to provide a theoretical framework as well as evidence to ascertain the pretest disease probability above which portable studies would be economically attractive as an initial test in the assessment of suspected OSA [70].

### ***Utilities of Multiple Sleep Latency Test (MSLT) in OSA***

MSLT is one of a few currently available de facto standard tests to measure physiological sleep tendency in the absence of external alerting factors. The test is based on the premise that the degree of sleepiness is correlated with and therefore reflected by sleep latency (the amount of time it takes for the individual to fall asleep) [71]. MSLT is usually ordered to diagnosis narcolepsy or other conditions of hypersomnia. The individuals with these conditions typically have reduced sleep-onset latency and early onset of REM sleep [71]. However, MSLT is occasionally indicated to quantify objectively sleepiness, e.g., residual daytime sleepiness despite presumed adequate CPAP treatment of OSA. For example, professional drivers or pilots with OSA may at times be subjected to medicolegal actions in order to objectify whether their residual sleepiness is significant enough to keep them off the roads. The test is usually done immediately following an overnight in-lab PSG in order to control for

the patient's sleep characteristics. The test asks the patient to have four or five naps (2 h between each) in a naturally dim-light environment during the day. The sleep onset latency is recorded for each nap. If the patient does not fall asleep within 20 min of each nap, the sleep onset latency is assumed to be 20 min. The average of the sleep onset latency is used as objective measure of sleepiness. With high test–retest reliability and inter-rater/intra-rater reliabilities, MSLT has demonstrated its ability to differentiate normal healthy subjects from those with pathologic sleepiness on both driving simulators as well as long-term road accidents [72, 73]. However, MSLT is not a reliable predictor of traffic accidents, emphasizing the need for more research in this area.

## Future Outlook

One of the ongoing research goals in OSA is to identify a relatively easily assayed biomarker. For example, recent studies have shown that amylase in saliva (i.e., salivary amylase activity as well as amylase mRNA levels) are elevated in individuals with EDS and OSA [74]. Among individuals with OSA, who are assumed to have higher sleep drive, systemic inflammation maybe involved in the pathogenesis of OSA [75]. Studies using microarrays looking at gene expression have shown that overnight expression of oxidative stress response genes such as antioxidant enzyme superoxidase dismutase 2 (SOD2) and catalase are up-regulated [76]. Proteomic analyses of serum and urine may yield future technique for identifying individuals with OSA. Even though there is a lack of data in adult population, recent findings suggest that proteins such as gamma-carboxyglutamic acid, perlecan, and gelsolin are differentially expressed among children with OSA and the control. Specific subpopulations of leukocytes such as TNF-alpha, IL-6, and some T lymphocytes have been found to be elevated among patients with OSA [77, 78]. Brief paroxysmal bursts of alpha activity have been identified before serious driving errors in simulation studies [79]. Similarly, a significant increase of eye blinks, in both number and duration, have been described before driving errors. Furthermore, an alteration of eyes blinking duration has been observed with increased driving time. With identification of more reliable biomarkers, the tasks of diagnosing OSA and sleepiness individuals will become less challenging.

## Summary Outline

- In clinic pretest screening questions (symptoms of snoring, daytime sleepiness, and common comorbidities) for OSA are important to efficaciously diagnose OSA. In some special clinical scenarios (i.e., occupational clinic), screening for OSA should rely more on objective anthropometric measurements.
- OSA risk factors include obesity, older age, male gender, postmenopausal status, Asian/African American races, tobacco, and alcohol use.



- The diagnostic criteria of sleep apnea are not uniform, but most of them try to characterize the frequency of sleep-disordered breathing events along with the degree of oxygen desaturation of each event.
- Three most commonly used diagnostic criteria for OSA are the AASM “Recommended” Criteria (or the “Medicare” Criteria), AASM “Alternative” Criteria, and “the Chicago” Criteria.
- There are four types of sleep studies available. Both in-lab PSG, or Type I, and portable monitors (PM), or Type II–IV, are being used for diagnosis of OSA. PSG is the gold standard test for diagnosis of OSA. PM offer a less-expensive and in-home alternative, with limitations in both sensitivity and specificity.
- A “split-night” study not only brings convenience to the patient by avoiding an extra evening of titration study but also reduces the overall cost for the diagnosis and treatment of OSA. A split-night study has become the “default” study type for individuals suspected of OSA.
- Whether an individual should undergo PM vs. PSG depends on the individual’s OSA risk factors, physical exam, medical comorbidities, suspicion of non-OSA sleep disorders, suspicion of any secondary gain/loss from the test result, and an overall pretest probability for OSA.

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# Chapter 4

## Approach to Hypersomnia

James A. Rowley

### Introduction

Hypersomnia or excessive daytime sleepiness is a major health problem in the United States, with several general surveys indicating that approximately one-third of Americans report daytime sleepiness at least a few days per month with approximately 6–8% reporting daily symptoms [1, 2]. Daytime sleepiness results in problems with vigilance, cognitive function, memory, concentration, and mood, generally leading to deterioration in school and/or job performance and productivity, social relationships and most importantly, driving skills. Driving drowsy is an increasingly prevalent problem. In the 2005 National Sleep Foundation survey, 60% of Americans reported driving a car while drowsy in the last year [3] while the 2009 poll found that 23% admitted driving drowsy at least once per month [4]. It has been estimated that up to 10–15% of accidents may be related to sleepiness or fatigue [5] with increasing severity of sleepiness associated with increased risk of an accident [6]. Therefore, an understanding of the causes and differential diagnosis of daytime sleepiness is important. This chapter will discuss the determinants of sleepiness, the commonly used methods of measuring sleepiness, the differential diagnosis and a practical approach to the diagnosis of sleepiness, with emphasis on which patients need referrals to a sleep center.

Before this discussion it would be helpful to first define abnormal daytime sleepiness. Secondary to circadian rhythms, sleepiness in the mid-afternoon is a normal phenomenon (see Determinants section below). Therefore, sleepiness at other times of the day or in situations in which alertness is warranted (meetings, lectures, driving)

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is generally considered abnormal. Another important concept is difference between physiologic and manifest sleep tendency. Physiological sleep tendency is the tendency to fall asleep in the absence of alerting factors and is determined by the factors discussed in the next section. In other words, sleepiness is also a physiologic state, similar to hunger or thirst [7, 8]. As such, the subjective feeling of sleepiness can be reduced by motivation, excitement, exercise, and other competing needs. Thus, manifest sleep tendency varies from moment to moment and is influenced by factors such as light, noise, and motivation. Reducing impinging stimuli or soporific conditions (such as reading or watching TV) serves to unmask the physiologic sleep tendency, not cause it. In other words, a truly alert individual would not be sleepy in a low stimulus environment.

## **Determinants of Daytime Sleepiness**

### ***Sleep Factors***

#### **Quantity of Sleep**

An individual's optimal sleep time is that time that allows him/her to maintain alertness throughout the day. For most individuals, this time is between 7 and 8 h each night. Even one night of sleep deprivation, generally to 4 h of sleep or less, can lead to increased sleepiness the following day [9]; this is a situation most individuals have experienced. More common, however, is chronic sleep deprivation, generally to less than 6 h per night over consecutive nights. Based upon two surveys, approximately 15–20% of Americans sleep less than 6 h per night on a regular basis; in addition, 20–30% of Americans reporting getting less than their required hours of sleep to feel refreshed and alert during the day [3, 4]. In analyses of the determinants of daytime sleepiness in two large cohorts, decreasing subjective total sleep time was associated with increased likelihood of subjective [1] or objective daytime sleepiness [10].

#### **Quality of Sleep**

The quality and continuity of sleep are important determinants of sleep. Sleep disorders that are characterized by brief arousals, such as the obstructive sleep apnea hypopnea syndrome (OSAHS), are examples of disorders that effect the quality of sleep and are associated with daytime sleepiness [11, 12]. However, other medical conditions, such as asthma, gastroesophageal reflux disease, and various pain syndromes, can also disrupt the continuity of sleep and possibly contribute to daytime sleepiness in these patient populations.

It should be noted, however, that studies do not universally indicate that there is a clear correlation between the degree of sleep discontinuity in OSAHS and the degree

**Table 4.1** Medication classes frequently associated with daytime sleepiness

Antihistamines
Benzodiazepines
Antidepressants
Narcotics
Alcohol
Barbiturates

of daytime sleepiness. For instance, in population studies, the prevalence of daytime sleepiness in subjects with OSAHS is low, ranging from 16 to 22% [13–16]. In the Pennsylvania cohort analysis, the apnea–hypopnea index was not found to be independent predictor of subjective excessive daytime sleepiness [1]. Finally, correction of the AHI by continuous positive airway pressure (CPAP) does not result in improvement in excessive daytime sleepiness in a large proportion of patients [17, 18].

**Circadian Rhythm**

A biphasic pattern of sleep tendency is observed when adults are testing for physiologic sleepiness by asking them to sleep at 2-h intervals in a low-stimulus environment, such as a darkened room [19]. As expected, the shortest latencies to sleep were observed during the early morning hours, 2–6 am. However, there was also shorter sleep latencies observed in the mid-afternoon, between 2 and 6 pm, corresponding to the time of day that many individuals will report an increased feeling of sleepiness and the time of the “siesta” prevalent in many cultures.

**Medications**

Several classes of medications can contribute to daytime sleepiness (see Table 4.1). The antihistamines, particularly those bought over the counter (such as diphenhydramine), are amongst the most common causes of sedation yet are often not thought of as drugs by patients and therefore not listed as medications when asked. Of the newer antihistamines, only cetirizine, which crosses the blood–brain barrier, is associated with daytime sleepiness.

Many psychoactive medications cause daytime sleepiness. While the benzodiazepine sedative hypnotics are generally taken at bedtime to help induce sleep, several of these agents are intermediate or long acting (temazepam and estazolam), and therefore can cause residual sleepiness during the day even when taken at bedtime. In addition, the anxiolytic benzodiazepines (diazepam, alprazolam) can cause sleepiness in some individuals. Several antidepressants, such as amitriptyline, trazodone, and paroxetine, have been associated with daytime sleepiness, as have barbiturates such as phenobarbital. Other drugs that have been associated with sleepiness include narcotic agents and alcohol.



## ***Demographic Factors***

### **Age**

Population studies have indicated that young age is associated with increased daytime sleepiness [1, 20]. In particular, in a large population study from Pennsylvania, using a subjective question regarding daytime sleepiness, found that young age (<30 years) and extreme older age (>75–80 years) are associated with an increased propensity to excessive daytime sleepiness [1]. The reasons underlying this finding are unclear, though the authors speculate that the increased propensity in the young is secondary to unmet sleep needs while in the extreme elderly it is related to increasing medical problems. Studies utilizing objective measures of sleepiness, such as the multiple sleep latency test (MSLT), have also shown that younger age is associated with increased propensity to daytime sleep [21, 22].

### **Gender**

Several studies [23, 24], though not all [1, 2], have shown that men have a higher propensity to sleepiness using subjective measures of sleepiness, such as the Epworth Sleepiness Scale (ESS). In addition, one study using the MSLT also showed that men had a higher propensity to sleep than women [10]. Reasons underlying this difference have not been systematically investigated, though the authors of at least one study using the Epworth hypothesized that women and men answer the questions differently and that the Epworth is more sensitive to sleepiness in men than woman [24].

### **Race**

Several large population and clinical cohorts have found that African-Americans have higher propensity to excessive daytime sleepiness as measured by the ESS [23, 25–27]. Authors of these studies have hypothesized that the higher Epworth in African-Americans could be due to shorter total sleep time [28] or an increased prevalence of sleep-disordered breathing in African-Americans [29]. In one of the studies, the authors found that the increased Epworth score in African-Americans was secondary to higher scores on just two of the items (#6 and #7, see Table 4.2); these data suggest there may be sociocultural differences that cause of the wording of the question to be interpreted differently by different groups. It should be noted that there have been no studies using objective measures of sleepiness to confirm the observed racial differences in the Epworth scale.

### **Obesity**

Several studies using subjective measures of sleepiness, including cohort [30, 31] and population studies [1], have indicated that obese patients are excessively sleepy



**Table 4.2** Situations in the Epworth sleepiness scale

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Sitting and reading
Watching TV
Sitting inactive in a public place (e.g., a theater or a meeting)
As a passenger in a car for an hour without a break
Lying down to rest in the afternoon when circumstances permit
Sitting and talking to someone
Sitting quietly after a lunch without alcohol
In a car, while stopped for a few minutes in traffic

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independent of the presence of sleep-disordered breathing. Studies using objective measures of sleepiness have confirmed these findings, generally showing that the increased propensity for daytime sleepiness occurs when the body mass index is  $>28\text{--}30\text{ kg/m}^2$  [10, 32]. Vgontzas and colleagues have proposed that obesity is related to sleepiness independent of OSAS because an interaction between increased cytokine release (particularly IL-6 and TNF- $\alpha$ ) and relative hypoactivity of the hypothalamic-pituitary axis, both of which are observed in obesity [33, 34]. There is also evidence that diabetes is independently associated with daytime sleepiness [1, 35]; therefore, insulin resistance may represent an additional mechanism that explains the association between obesity and sleepiness.

### ***Pathology of the Central Nervous System***

A normally functioning nervous system, particularly in the areas that control the wakefulness-sleep cycle is critical. Narcolepsy is the best example as it has been shown that the destruction of hypocretin-secreting neurons in the posterior hypothalamus, which is now understood to be the primary pathologic finding in narcolepsy [36].

## **Measurement of Daytime Sleepiness**

### ***Multiple Sleep Latency Test (MSLT)***

The MSLT measures the physiologic sleep tendency by measuring the latency to sleep in the absence of alerting factors such as noise and light [7, 22]. During the test, which is generally performed the day after a full night sleep study, the patient is instructed to fall asleep in bed, in a dark, quiet room at 2-h intervals 5 times during the day beginning 1.5–2 h after awakening. Naps are terminated either at 20 min if there is no sleep or 15 min after the onset of sleep. The latency to sleep for each nap is defined as the time from the start of the test to the first 30-s epoch of any stage of sleep. The individual latencies are then averaged determining the mean daytime

sleep latency. Generally, mean latencies greater than 15 min are considered normal; a sleep latency  $\leq 5$  min is considered severe or pathologic. In addition, there should be no rapid-eye movement (REM) sleep during any of the nap opportunities. The reader is referred to the American Academy of Sleep Medicine practice parameter for complete guidelines for the optimal performance of the MSLT [37].

The MSLT has been shown to be a valid and reliable test of daytime sleepiness [22, 38]. It correlates with reported total sleep time [10] and it can detect changes in sleepiness secondary to acute changes in sleep time [7], and drugs such as caffeine and alcohol [39–41]. It also appears to be sensitive to the treatment of sleep disorders such as obstructive sleep apnea [17, 42] and narcolepsy [43], though this is not a universal finding [17, 44].

The MSLT is considered essential in the evaluation of patients with suspected narcolepsy. Patients with narcolepsy generally have pathologic sleep latencies ( $< 5$  min) and have a sleep onset REM period (SOREMP) on at least two of the five naps. Summary analysis shows that the presence of two or more SOREMPs on a MSLT has a sensitivity of 0.78 and a specificity of 0.93 for the diagnosis of narcolepsy [22]. Thus, in the absence of cataplexy, the presence of two or more SOREMPs is considered diagnostic of narcolepsy. It should be noted that two or more SOREMPs have been noted in up to 13% of the general population [45] and in approximately 5% of patients with OSA [46]. Thus, the presence of SOREMPs on a MSLT should be considered within the overall clinical context of each individual patient.

The primary disadvantage of the MSLT is lack of discrimination between normal and sleepy populations because of a wide range of normal values. In an analysis of published studies performing the MSLT in normal populations, the authors found that the mean latency for the five-nap MSLT for normal subjects  $11.6 \pm 5.2$  min [22]. Using a two-standard deviation to determine a normal range, the normal range for controls would be 1–20 min, which is clearly not discriminatory. Another disadvantage of the MSLT is that it is laboratory based, requiring trained sleep personnel to perform.

Based upon the strengths and limitations above, the American Academy of Sleep Medicine has identified indications for performing the MSLT [37]. Indications that were recommended as a standard of care (highest level of care) were: (1) the use of the MSLT as part of the evaluation of patient with suspected narcolepsy to confirm the diagnosis; and (2) repeat MSLT is indicated if suspected narcolepsy but first test was inadequate or did not provide confirmation of the diagnosis. The committee felt that the MSLT may be indicated in the evaluation of a patient with suspected idiopathic hypersomnia to differentiate from narcolepsy. Finally, the MSLT is not routinely indicated in the evaluation or management of OSA, insomnia, or circadian rhythm disorders.

### ***Maintenance of Wakefulness Test (MWT)***

While the MSLT is a test of physiologic sleepiness, the maintenance of wakefulness test (MWT) is a test of manifest sleepiness as it tests the ability of the patient to stay awake

in a low stimulus environment. The MWT is felt to be more clinically relevant as it more closely reflects the challenge patients face in soporific situations of everyday life. The MWT protocol is similar to that of the MSLT (4 naps, spaced 2 h apart) except that the patient is instructed to stay awake while sitting upright in a low-stimulus environment (light level up to 0.13lux [equivalent of 7.5 W light bulb]). In the MWT, individual tests are terminated at 40 min if no sleep occurred or there is three consecutive epochs of stage N1 sleep or any epoch of any other stage of sleep. Similar to the MSLT, sleep is defined as the time from the beginning of the test until the first epoch of any stage of sleep. Latencies from the four naps are then averaged to give a mean onset latency.

Mean latencies for the MWT have been shown to be longer than mean latencies for the MSLT for both normal subjects [22] and patients with sleep apnea [44, 47] and narcolepsy [48] confirming that the MWT is measuring a different aspect of sleepiness than the MSLT. However, the degree of correlation between the MSLT and MWT, while significant, is small [48, 49]. The MWT is sensitive to treatment effects, having been shown to improve with the treatment of OSA with CPAP [47, 50] and with modafinil for narcolepsy [51]. One older study indicated that the MWT may be more sensitive for treatment effects in sleep apnea as there was a significant increase in the mean latency for the MWT but not for the MSLT with CPAP [44].

The MWT has been proposed as a clinical test to determine if a subject can safely operate a car, truck, or airplane. The limited number of studies on the predictive role of the MWT for driving safety have found that a shorter sleep latency on the MWT correlates with decreased performance on a driving simulator [52, 53]. However, the evidence for the predictive ability of the MWT for real-world driving is less clear [47, 54], and there is evidence that performance on a driving simulator performance does not correlate with real-world driving [55], limiting the value of the MWT for predicting driving safety. Nonetheless, the Federal Aviation Administration requires the MWT for pilots with sleep disorders to certify that they are safe to fly commercial airplanes [56].

Similar to the MSLT, a disadvantage of the MWT is a wide range of normative values. In an analysis of published studies performing the MWT in normal populations, the authors found that the mean latency for the MWT is  $30.4 \pm 11.2$  min [22]. Thus, the cutoff value of a normal study is not clear, limiting applicability, particularly for the evaluation of workplace safety. Also, there is evidence that the MWT is susceptible to changes in motivation [57, 58].

Based upon the strengths and limitations above, the American Academy of Sleep Medicine has identified indications for performing the MWT [37]. The MWT may be indicated to assess an individual's ability to remain awake when his/her ability to remain awake constitutes a public or personal safety issue or to assess the effect of treatment in individuals with excessive daytime sleepiness.

### ***Epworth Sleepiness Scale (ESS)***

The ESS was developed as an easy to use scale to objectively measure daytime sleepiness without the requirement for in-laboratory testing [8, 59, 60]. The ESS was

designed to measure the general level of excessive daytime sleepiness or sleep propensity in adults. As developed, it was intended to measure daytime sleepiness that persists over periods of more than 1 week, independent of changes in time of day and from day to day. In addition, it was designed to overcome the fact that different individuals will have different routines, some that facilitate and others that inhibit sleep. In addition, it asks for the likelihood of falling asleep in different situation. It does not ask how often someone falls asleep in a certain situation as the answer would depend on how often the individual finds him/herself in that situation.

In answering the ESS, the patient rates his/her likelihood of dozing off in eight situations (Table 4.2) which range from highly soporific (watching TV or reading) to those requiring attention (talking to someone, sitting in a meeting). Each situation is scored on a scale of 0, will not doze off, to 3, high likelihood of dozing off; the scores from each situation are added, giving a final score between 0 and 24. Traditionally, a score of 10 or above has been used to distinguish between individuals with and without daytime sleepiness, though evidence from one study suggested that a cutoff of 12 may more reliably indicate an increased tendency to fall asleep on the MSLT [10]. Most studies have suggested that the ESS has good test–retest reliability [60–62] though one group found that while the mean ESS was similar over time there was actually a large degree of variation between individuals [63]. Studies have shown that the ESS correlates with different sleep disorders [64] and has been found to correlate with severity of OSAHS [8, 12].

There are several limitations to the ESS [65]. The major limitation of the ESS is that it does not correlate well with the MSLT. In other words, while a higher ESS score indicates a greater propensity to fall asleep on the MSLT [10], a higher score does not necessarily predict a shorter sleep latency on the MSLT [66, 67]. For instance, in a group of 102 patients evaluated for excessive daytime sleepiness, primarily patients with sleep-disordered breathing, 68% of patients with a normal sleep latency on the MSLT had an ESS score  $\geq 10$  while 36% of patients with a sleep latency  $< 5$  min on the MSLT had a ESS  $< 10$ . Therefore, on initial evaluation, the ESS may or may not indicate that the patient is truly sleepy as measured objectively by the MSLT. In addition, the ESS also does not ask about other situations in which the propensity for sleep may be important (such as work) nor does it include questions about naps. The noninclusion of naps is important as many sleep physicians have found that some patients will have low ESS scores but report multiple naps per day. Contextual factors are another potential limitation. In a study of 146 subjects, the answer to individual items on the ESS was shown to be influenced by contextual factors such as position (lying down v. sitting up), location (public v. private), and interest level (interesting v. boring) [68]. For instance, a patient lying in bed watching TV was more likely to rate a higher propensity to falling asleep than a patient watching TV sitting up. While these contextual elements are not present in the ESS as presented to patients, these results suggest that different individual patients may interpret the situations in different contexts, which could alter scores. Finally, the ESS was developed and has been primarily validated in white populations. While it has been validated in other populations and non-English cultures [61, 62], it is unclear if the ESS measures sleepiness consistently between groups or if different

groups could interpret individual items differently. For instance, differing interpretation of items #6 and 7 on the ESS was found in a study comparing the ESS between whites and African-American populations [25]. In addition, there is evidence that men and women will answer the Epworth differently; in the Sleep Heart Health Study, men and women equally reported daytime sleepiness when asked as a simple yes/no question but women had an overall lower Epworth than men [24].

While the ESS may not provide an accurate indication of which individuals are sleepy, there are several studies that show that higher ESS scores decrease with effective treatment of the primary sleep disorder, including OSAHS and narcolepsy [17, 51, 69]. In other words, the ESS can provide valuable information to the physician in determining whether the treatment plan has been effective for the patient and it is widely used for this purpose.

### ***Summary of Measurements of Excessive Daytime Sleepiness***

In summary, there are three standard measurements of excessive daytime sleepiness, the MSLT, MWT, and ESS. All three tests have advantages and limitations for their use in the evaluation of excessive daytime sleepiness, including evaluation of workplace safety. The evidence suggests that these tests likely measure different aspects of sleepiness, do not correlate well with each other [48, 49, 66, 70], and respond differently to treatment [17]. Thus, no test should be considered “gold standard” [70] and the individual test chosen to evaluate sleepiness in any individual patient should be chosen based upon the needs of the evaluation (for instance, a MSLT if narcolepsy suspected; a MWT for an airline pilot seeking certification to fly).

### **Differential Diagnosis**

The differential diagnosis of excessive daytime sleepiness is presented in Table 4.3. Key symptoms and characteristics of each are briefly presented in this section.

Chronic insufficient sleep is probably the most common of these diagnoses given the prevalence of sleep deprivation in adults [3, 4], but is an infrequently made diagnosis because chronic sleep deprivation is not looked upon as a medical problem. The two major characteristics of chronic insufficient sleep are habitual sleep episodes that are shorter in duration than expected for age (generally 7–8 h for adults) and longer than normal sleep episodes on weekends or vacations. Other clues to diagnosis include patient’s work schedule, number of jobs, family and other social obligations, and hours of television and internet use. Chronic insufficient sleep is a clinical diagnosis based upon the patient’s sleep and social history. However, many patients with other sleep disorders also have insufficient sleep. Therefore, it is important to consider other causes before considering chronic insufficient sleep the primary reason for a patient’s daytime sleepiness. In addition, in patients with other

**Table 4.3** Differential diagnosis of daytime sleepiness

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Behaviorally induced insufficient sleep syndrome
Obstructive sleep apnea
Narcolepsy
Restless leg syndrome/periodic limb movement disorder
Disorders of the sleep–wake cycle
Sleep phase delay syndrome
Shift work
Idiopathic hypersomnia
Drug effect

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disorders who report continued daytime sleepiness despite ongoing primary therapy for that disorder, should be evaluated for the presence of chronic insufficient sleep.

OSAHS is characterized by recurrent collapse of the upper airway during sleep; the episodes of collapse are associated with oxyhemoglobin desaturation and recurrent arousals [71, 72]. Patients generally present with the complaint of loud snoring that is bothersome to the bed partner, witnessed apneas, nocturnal, gasping and choking, morning headaches, and nonrefreshing sleep. OSAHS is diagnosed by polysomnography; therefore, referral to a sleep center for diagnostic testing is generally recommended.

Narcolepsy is a chronic neurologic condition characterized by both excessive daytime sleepiness and impaired regulation of REM sleep [73, 74]. Pathologically, narcolepsy is associated with destruction of hypocretin-producing neurons in the hypothalamus and decreased hypocretin in the cerebrospinal fluid [36, 75, 76]. Narcolepsy is also tightly associated with the human leukocyte antigen DQB1\*0602 [77]. In addition to the daytime sleepiness, narcoleptic patients often have cataplexy, hypnagogic hallucinations, and sleep paralysis. Cataplexy, considered pathognomonic of this disorder, is sudden muscle weakness brought on by intense emotion such as laughter or anger. The muscle weakness can affect any muscle group and manifest as falling, facial or head droop, or dropping objects. Hypnagogic hallucinations, intense dream-like hallucinations, at the beginning of the night soon after the patient falls asleep, and sleep paralysis, profound weakness of the skeletal muscles generally occurring during awakenings during the night, are not specific to narcolepsy; both have been reported by patients with severe obstructive sleep apnea, and idiopathic hypersomnia while sleep paralysis can also occur as a sporadic parasomnia. Because both a nocturnal sleep study and a MSLT are required for the diagnosis of narcolepsy, referral to a sleep center is recommended.

The restless leg syndrome (RLS) is characterized by a (1) feeling of motor restlessness or urge to move the legs; (2) relief with leg movement; (3) restlessness occurs primarily while legs are relaxed (sitting with legs reclined or lying down); (4) restlessness occurs primarily in the evening [78, 79]. RLS is often associated with recurrent leg kicking during sleep, the main characteristic feature of periodic limb movement disorder (PLMD). RLS often presents as insomnia because the restlessness prevents the patient from falling asleep; however, if there are prominent leg

movements, daytime sleepiness can be the presenting symptom. RLS is a clinical diagnosis, requiring only the presence of the four major symptoms noted and is generally treated with dopaminergic agents.

In general, disorders of the sleep–wake cycle are characterized by a misalignment between the patient’s sleep cycle and the society norm (which is generally a bedtime between 10 pm and midnight with awakening between 6 and 8 am) [80, 81]. Most shift workers, particularly those with night shifts or frequently rotating shifts, will complain of excessive daytime sleepiness because it is difficult to achieve normal sleep when the major sleep episode begins in the morning. Patients with sleep phase delay syndrome tend to go to bed after midnight (bedtime is delayed relative to societal norm) and if allowed, will generally sleep uninterrupted for 7–8 h, awakening refreshed. The shifted sleep pattern becomes abnormal when the patient must awaken earlier than his/her usual time, generally because of employment; the shortened sleep time leads to insufficient sleep and excessive sleepiness.

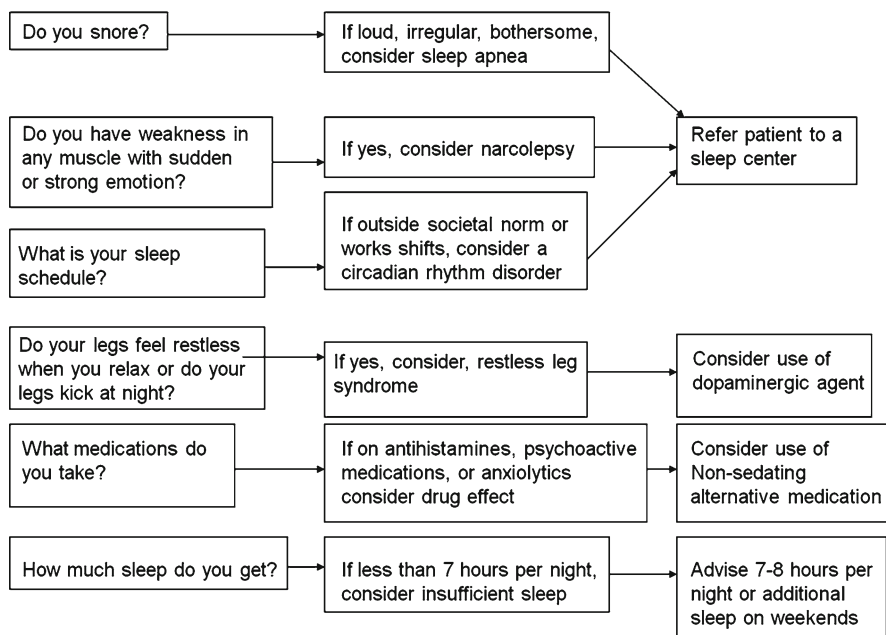
Idiopathic hypersomnia is characterized by constant daytime sleepiness and frequent daytime sleep episodes lasting 1 h or more that are generally not refreshing [82–84]. The MSLT demonstrates moderate to severe shortening of the daytime sleep latency (<10 min) but there is generally no REM sleep during any of the naps. Idiopathic hypersomnia is a difficult diagnosis to make as symptoms and findings overlap with other disorders, particularly narcolepsy. It is generally diagnosed only after patients have had a full sleep evaluation, including a sleep log, polysomnography, and a MSLT, and other causes of daytime sleepiness, particularly chronic insufficient sleep, OSAHS, narcolepsy, and RLS, have been ruled out.

## Approach to the Sleepy Patient

A systematic approach to the patient presenting with excessive daytime sleepiness is important to both recognizing and managing these patients. Patients identified as possibly having obstructive sleep apnea or narcolepsy should be referred to a sleep center for optimal diagnosis and treatment. Other patients, particularly those on medications associated with sedation or not getting sufficient sleep, can be counseled and managed by the primary care physician.

Identification of these patients begins with asking every patient if they are excessively sleepy during the day. If the answer is “yes,” there are six simple follow-up questions to be asked (outlined in Fig. 4.1).

1. Do you snore? If the answer is yes and the snoring is loud, habitual, and bothersome, obstructive sleep apnea is likely. Referral to a sleep laboratory for a sleep study is recommended in all of these patients.
2. Do your legs feel restless when you relax or do your legs kick at night? If the answer is yes, RLS should be considered. A trial of a dopamine agonist such as ropironole or pramipexole is recommended with referral to a sleep specialist if not successful.



**Fig. 4.1** Approach to the patient with daytime sleepiness

3. Do you have weakness in your muscles with sudden or strong emotion such as laughter? This question attempts to identify cataplexy, the pathognomonic symptom of narcolepsy. If the patient has cataplexy or any of the other major symptoms of narcolepsy (automatic behaviors, sleep paralysis, or hypnagogic hallucinations), referral to a sleep center for a sleep study and MSLT is recommended.
4. What is your sleep schedule? If the patient's sleep schedule is outside the societal norm (to bed 10 pm to midnight, out of bed 6–8 am), or the patient works shifts, a sleep–wake cycle disorder must be considered. Referral to a sleep center is recommended.
5. What medications do you take? The physician should obtain a complete medication list, including common over-the-counter agents. If the patient is taking a medication associated with daytime sleepiness (Table 4.1), the physician should make a therapeutic substitution if possible.
6. Do you sleep much longer on weekends or on a vacation? Most individuals who are sleep deprived attempt to make up for the lost sleep by “sleeping in” on weekends or during vacations. These individuals will often report less sleepiness after obtaining the additional sleep. Individuals who are chronically sleep deprived should be counseled regarding the importance of regular sleep and of obtaining at least 7–8 h of sleep per night.



In summary, individuals with symptoms consistent with one of the major sleep disorders, such as obstructive sleep apnea or narcolepsy should be referred to a sleep center for diagnosis and management. Individuals with symptoms consistent with drug effect or chronic insufficient sleep can be initially counseled by their primary physician. If a medication change or additional sleep does not result in improvement in the daytime sleepiness, referral to a sleep center is recommended.

## Summary of Keypoints

- Hypersomnia is defined as sleepiness during times of the day or during situations in which alertness is warranted.
- Sleep factors that influence hypersomnia include quantity of sleep, quality of sleep, and circadian rhythms.
- Medications associated with hypersomnia include benzodiazepines, antihistamines, many antidepressants and antipsychotics and narcotics.
- Demographic factors that are clearly associated with hypersomnia are younger age and obesity. Males and African-Americans may also be predisposed to increased daytime sleepiness.
- The MSLT is an objective measure of physiologic sleep propensity. While the MSLT is generally reliable and valid, it has poor discriminatory value and is primarily used to diagnose narcolepsy.
- The MWT is an objective measure of manifest sleep propensity. The MWT is primarily used to determine if patients in high risk jobs (such as truck drivers or pilots) can remain awake for sustained periods.
- The ESS is a subjective measurement of sleep propensity. While considered a valid and reliable test, it does not correlate with the MSLT and is best used to measure response to therapy.
- Differential diagnosis of hypersomnia includes insufficient sleep, sleep-disordered breathing, narcolepsy, RLS, shift work, delayed sleep phase syndrome, and medication effect.

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# Chapter 5

## Obstructive Sleep Apnea: Epidemiology of Sleep Apnea

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**Keywords** Sleep apnea, obstructive • Polysomnography • Epidemiology • Prevalence • Risk factors • Disease progression • Lung

### Introduction

The most common sleep disorders in the clinic are those falling into the category of sleep-disordered breathing, which comprises a group of conditions characterized by intermittent cessations (apneas) or reductions (hypopneas) in respiration during sleep. These events can result from either the absence of ventilatory drive (central sleep apnea), or a physical blockage occurring in the upper airway during which there are still attempts to breathe (obstructive sleep apnea; OSA). In the laboratory, central and obstructive apneas can be easily distinguished as the former are accompanied by an absence of respiratory effort, whereas the latter are accompanied by ongoing (often out-of-phase) thoracic and abdominal movements. Although it is more straightforward to think of central sleep apnea and OSA as separate diseases with discrete etiologies, many patients exhibit both types of events hence there are likely to be shared pathophysiologic mechanisms.

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The spectrum of obstructive sleep-disordered breathing has historically been described as ranging from simple snoring, through upper airway resistance syndrome (UARS), to full-blown OSA. While the idea of a spectrum has its merits, it suggests that simple snoring is benign, which recent evidence indicates may not be the case [1]. This concept also implies that over time an individual progresses from being normal to developing simple snoring then UARS and then finally OSA. Thus far, there are insufficient longitudinal data to confirm or refute this supposition. UARS is most often defined as the presence of frequent respiratory effort-related arousals (RERAs), arousals from sleep due to increased work of breathing secondary to increased airway resistance where the reduction in airflow is insufficient to meet criteria for hypopnea. Whether UARS is a clinical entity separate from, or simply a milder form of, clinically defined OSA is debatable. Laboratories which use relatively strict criteria for defining hypopnea (i.e., based on 4% O<sub>2</sub> desaturation) frequently score RERAs, whereas laboratories using more liberal criteria (i.e., discernable decrement in flow with either desaturation or arousal) essentially never observe RERAs.

The repeated occurrence of obstructive apneas and hypopneas overnight leads to a predictable pattern of events: a reduction of inspiratory airflow leading to episodic hypoxemia and hypercarbia, an increase in respiratory effort, arousals in order to restore normal respiration, fragmented sleep, and in many cases excessive daytime sleepiness. Many published papers refer to OSA syndrome (OSAS) to describe obstructive respiratory events in the presence of daytime hypersomnolence. Because OSA can be detected overnight in patients who do not report sleepiness, the prevalences of OSA and OSAS differ substantially (discussed below). However, recent research has highlighted the potential importance of “asymptomatic” OSA in terms of cardiovascular risk leading some to question the utility of the OSAS term.

The gold-standard diagnostic test for OSA is full-night polysomnography (PSG) where simultaneous measurements of cortical activity, eye movements and muscle tone are made to determine sleep staging as well as respiratory airflow and effort, pulse oximetry, and electrocardiography to identify respiratory and cardiac abnormalities. In situations where the use of full PSG is not feasible, a limited-channel cardio-respiratory or oximetry study may also be used as diagnostic tools.

The main index by which OSA severity is judged is the apnea-hypopnea index (AHI) – the number of apneas and hypopneas per hour of sleep. Limited-channel recordings do not typically measure sleep/wake status and so use hours of recording time for the denominator. Thus, if there is substantial time spent awake on such a recording, the resulting AHI may be artifactually reduced. Nevertheless, the distinction between an AHI based on hours of sleep or on hours of recording is often overlooked.

## Clinical Definitions of Obstructive Sleep Apnea

The clinical definition of OSA is constantly evolving, and there is still no clear consensus as to how to define the disease. There are a number of inconsistencies in PSG methodology and the criteria used to score them, which makes comparisons of data over time and between laboratories difficult.

In particular, the scoring criteria used to identify respiratory events are not widely agreed upon. In 1997, a task force established by the American Academy of Sleep Medicine (AASM) met in Chicago to develop consensus criteria for defining respiratory events and diagnosing OSA in order to facilitate comparability of studies for research purposes [2]. These criteria, known as the Chicago criteria, were quickly adopted by researchers around the world. However, an updated scoring manual encompassing sleep stages, arousals and respiratory events was released by the AASM in 2007 [3], and although it has become a requirement for sleep laboratory accreditation in the United States, the Chicago criteria are still in widespread use internationally (see Table 5.1 for a comparison of the Chicago and updated AASM criteria).

There are a number of key differences between the two sets of scoring rules. The most notable difference is that the updated rules include two definitions of hypopnea: the recommended definition is a reduction in thermal sensor amplitude of  $\geq 30\%$  from baseline for  $\geq 90\%$  of the event’s duration ( $\geq 10$  s) accompanied by a

**Table 5.1** A comparison of respiratory event scoring according to Chicago 1999 and AASM 2007 criteria

	Chicago criteria 1999 [2]	AASM criteria 2007 [3]
OSAS	Must fulfill A or B, plus C	None
diagnostic criteria	A. Excessive daytime sleepiness <sup>a</sup> B. Two or more of the following <sup>a</sup> <ul style="list-style-type: none"><li>• Choking or gasping</li><li>• Recurrent awakenings</li><li>• Unrefreshing sleep</li><li>• Daytime fatigue</li></ul> C. AHI $\geq 5$ events/h of sleep	
Event definitions	Must fulfill A or B or C, plus D A. Apnea <ul style="list-style-type: none"><li>• <math>&gt;50\%</math> decrease in breathing amplitude</li></ul> B. Hypopnea <ul style="list-style-type: none"><li>• A clear but <math>&lt;50\%</math> decrease in breathing amplitude, plus O<sub>2</sub> desaturation <math>&gt;3\%</math> or an arousal</li></ul> C. Respiratory effort-related arousal (RERA) <ul style="list-style-type: none"><li>• Increasingly negative esophageal pressure, terminated by a sudden increase in pressure and an arousal</li></ul> D. $\geq 10$ s duration	Must fulfill A or B or C, plus D A. Apnea <ul style="list-style-type: none"><li>• <math>\geq 90\%</math> decrease in breathing amplitude for <math>\geq 90\%</math> of event duration</li></ul> B. Hypopnea <ul style="list-style-type: none"><li>• <i>Recommended:</i> <math>\geq 30\%</math> decrease in breathing amplitude for <math>\geq 90\%</math> of event duration, plus O<sub>2</sub> desaturation <math>\geq 4\%</math></li><li>• <i>Alternative:</i> <math>\geq 50\%</math> decrease in breathing amplitude for 90% of event duration, plus O<sub>2</sub> desaturation <math>\geq 3\%</math> or an arousal</li></ul> C. RERA: no change from Chicago D. $\geq 10$ s duration

(continued)



**Table 5.1** (continued)

	Chicago criteria 1999 [2]	AASM criteria 2007 [3]
Technical aspects	<p>Pneumotachometer is considered the gold standard for measuring airflow.</p> <p>In its absence, two independent respiratory measurements should be recorded; highest recommendation is given to nasal pressure and respiratory inductance plethysmography of chest and abdominal movement.</p> <p>RERAs must be identified using esophageal pressure</p>	<p>Identification of apnea with thermal sensors; identification of hypopnea with nasal pressure. Identification of RERAs with esophageal pressure, but nasal pressure or respiratory inductance plethysmography of chest and abdominal movement are valid alternatives</p>
Severity	<p>Syndrome defined as the more severe of A or B</p> <p>A. Daytime sleepiness</p> <ul style="list-style-type: none"> <li>• Mild (occurring during activities requiring little attention)</li> <li>• Moderate (occurring during activities requiring moderate attention)</li> <li>• Severe (occurring during activities requiring active attention)</li> </ul> <p>B. Overnight monitoring</p> <ul style="list-style-type: none"> <li>• Mild (5 to &lt;15 events/h)</li> <li>• Moderate (15 to &lt;30 events/h)</li> <li>• Severe (<math>\geq 30</math> events/h)</li> </ul>	None

<sup>a</sup>Not better explained by other factors

$\geq 4\%$   $O_2$  desaturation from baseline, or alternatively a  $\geq 50\%$  reduction in thermal sensor amplitude accompanied by a  $\geq 3\%$   $O_2$  desaturation from baseline or terminated by an arousal. Thus, the recommended definition focuses only on desaturation with no importance given to arousal from sleep. A recent study compared the AHI for 328 patients when scored using the three definitions of hypopnea, and reported that the median AHI obtained using the 2007 recommended and alternative criteria were 30 and 60%, respectively, of the median AHI obtained using Chicago criteria [4]. Hence, both the recommended and alternative hypopnea definitions of the 2007 AASM rules are stricter than the Chicago definition.

At present, there is no agreement as to the use of either nasal pressure or thermal sensors to identify respiratory events. The Chicago rules recommend that in the absence of a pneumotachometer, two independent measurements of airflow should be used. The highest evidence-based recommendation is given to nasal pressure and respiratory inductance plethysmography, though it is noted that limited data were available on which to base a firm recommendation. Nasal pressure is often preferred to thermistors due to its improved sensitivity; however, the specificity of this technique has been minimally studied. In addition, thermistor is preferred to

nasal pressure for the distinction between hypopnea and apnea. More respiratory events are detectable using nasal pressure [5], leading to a higher AHI than when thermal sensors are used.

The Chicago criteria focus on OSAS and include excessive daytime sleepiness as a component of the diagnosis whereas the 2007 AASM criteria do not mention OSAS and focus on OSA alone. The proposition of expanding the diagnostic criteria of OSA to include asymptomatic patients has gained popularity in recent years, as there appears to be no significant difference in long-term cardiovascular mortality risk between sleepy and nonsleepy patients [6]. However, the consequences of asymptomatic OSA on other outcomes remain controversial [7, 8].

The updated 2007 scoring criteria do not include a definition of OSA severity; in practice this means that the AHI severity thresholds detailed in the Chicago criteria are often used with the updated AASM scoring rules, despite the fact that the AHI will be markedly different depending on the methodology and scoring approach adopted. Using the 2007 AASM criteria could result in a positive Chicago diagnosis becoming negative in up to 40% of patients [4], emphasizing the need for new normative values to be calculated using the more recent scoring criteria. Conversely, the 2007 AASM rules allow for the diagnosis of asymptomatic OSA, leading to a far greater number of positive cases. Ideally, the clinical definition of OSA should be chosen based on rigorous research demonstrating the ability to predict adverse effects and positive response to treatment. At this stage, however, there is insufficient evidence available for a consensus to be reached. Moreover, AHI is poorly predictive of many OSA complications, leading to uncertainty about severity criteria and generating interest in developing new outcome measures [9, 10].

## Prevalence

OSA represents a major public health burden, and yet there is little doubt that the disease remains enormously under-diagnosed [11]. The most widely cited OSA prevalence study is now outdated by over 15 years [12] and the prevalence of obesity – a major risk factor for OSA – has increased markedly over the intervening period [13]. Additionally, some of the methodological inconsistencies mentioned above, most notably the use of the narrower definition of OSAS rather than OSA, contributes to confusion about the true prevalence of this disorder.

Performing PSG studies in a research setting is costly; many epidemiological studies using PSGs have small sample sizes, while larger studies have tended to use alternative monitoring methods. The methodology of existing epidemiological studies has also differed in terms of sampling strategies, respiratory event definition, and criteria for diagnosing OSA making combining international datasets impossible. Given that the risk factors of OSA (discussed further below) can be more or less common in certain areas of the world, it is perhaps more appropriate to consider each epidemiological study individually (see Table 5.2).

Table 5.2 Major OSA prevalence studies

Region	First author (year) location	Population studied	Total screened/ recorded	Age range (years)	Methods	Airflow measure	Scoring rules	Criteria for OSA	Male prevalence (%)	Female prevalence (%)
North America	Young (1993) [12], Wisconsin, USA	State employees	3,513/602	30–60	Questionnaire Full laboratory PSG	Thermocouple + end-tidal CO <sub>2</sub>	Modified Chicago <sup>a</sup>	AHI ≥ 5 + symptoms AHI ≥ 15 AHI ≥ 5	4.0	2.0
	Bixler (1998) [14], Pennsylvania, USA	General population; males	4,364/741	20–100	Telephone interview Full laboratory PSG	Thermocouple	Modified Chicago <sup>a</sup>	AHI ≥ 10 + symptoms OA/HI ≥ 15	3.9	7.2
	Bixler (2001) [15], Pennsylvania, USA	General population; females	12,219/1,000	20–100	Telephone interview Full laboratory PSG	Thermocouple	Modified Chicago <sup>a</sup>	AHI ≥ 10 + symptoms OA/HI ≥ 15	1.2	2.2
Europe	Duran (2001) [16], Basque Country, Spain	General population	2,148/555	30–60	Home interview Four-channel monitoring at home Full laboratory PSG	Thermistor	Modified Chicago <sup>a</sup>	AHI ≥ 5 + symptoms AHI ≥ 10	3.4	3.0
									19.0	14.9
Asia	Ip (2001) [17], Hong Kong, China	Office workers; males	784/150	30–60	Questionnaire Full laboratory PSG	Thermistor	Modified Chicago <sup>a</sup>	AHI ≥ 5 + symptoms AHI ≥ 5	4.1	8.8
	Ip (2004) [18], Hong Kong, China	Office workers; females	854/106	30–60	Questionnaire Full laboratory PSG	Thermistor	Modified Chicago <sup>a</sup>	AHI ≥ 5 + symptoms AHI ≥ 5	2.1	3.7

South America	Kim (2004) [19], Ansan, Korea	General population	5,020/457	40–69	Questionnaire Full laboratory ( <i>n</i> = 335) or home PSG ( <i>n</i> = 137)	Thermistor	Modified Chicago <sup>a</sup>	AHI ≥ 5 + symp- toms	4.5	3.2
								AHI ≥ 5	27.1	16.8
								AHI ≥ 5 + symp- toms	4.0	1.5
South America	Reddy (2009) [20], South Delhi, India	General population	2,505/365	30–65	Questionnaire (translated) Full laboratory PSG	Thermistor	Standard Chicago	AHI ≥ 5	13.5	5.5
								AHI 5–15 + symptoms	40.6	26.1
								or AHI ≥ 15	46.5	30.5
Australasia	Bearpark (1995) [22], Busselton, Australia	General population; males	486/294	40–65	Questionnaire Four-channel monitoring at home	None	O <sub>2</sub> desat ≥ 3% + HR increase or snoring	AHI ≥ 5 + symp- toms	3.1	
								AHI ≥ 5	25.9	
New Zealand	Mihaere (2009) [24], Wellington, New Zealand	General population	705/358	30–59	Questionnaire Four-channel monitoring at home	None	O <sub>2</sub> desat ≥ 4% + HR increase or snoring	AHI ≥ 15	3.9	0.2
								AHI ≥ 10	7.0	1.4
								AHI ≥ 5	12.5	3.4

<sup>a</sup>Modified Chicago: Standard Chicago rules [2], but using 4% O<sub>2</sub> desaturation to score hypopnea and no scored RERAs

## *North America*

To date, two large USA-based OSA prevalence studies have been performed using in-laboratory PSG methodology: the Wisconsin and Pennsylvania cohorts. Both studies recruited predominantly Caucasian participants.

The Wisconsin Sleep Cohort Study was initiated in 1988 by sending a questionnaire based on general sleep patterns to state employees aged 30–60 years, and using this to identify those who reported habitual snoring, snorting, breathing pauses or episodes of loud snoring [12]. Out of the participants who returned the questionnaires ( $n=3,513$ ), all of those reporting the above symptoms were recruited into the study proper, along with 25% of those who did not report these symptoms in order to gain a population with adequate variance. This population ( $n=625$ ) went on to have an overnight in-laboratory PSG, with nasal and oral airflow measured using thermocouples and end-tidal  $\text{CO}_2$ , respectively; data were obtained for 602 participants. The Wisconsin study took place before the publication of the Chicago criteria; the scoring rules adopted were similar and have since been referred to as “modified Chicago” – a 4%  $\text{O}_2$  desaturation to define hypopnea rather than 3%, and RERAs not scored. The prevalence of OSAS defined as an  $\text{AHI} \geq 5/\text{h}$  as well as self-reported daytime sleepiness was 2% in women and 4% in men, but including asymptomatic participants ( $\text{AHI} \geq 5/\text{h}$  only), the overall prevalence was 9% in women and 24% in men. For moderate to severe OSA ( $\text{AHI} \geq 15/\text{h}$ ), the prevalences were 4% in women and 9% in men. Because thermistor but not nasal pressure was used to define respiratory events, one would predict even higher prevalences if the study was done with current technology.

The Pennsylvania cohort was first reported in 1998 using males only [14], and later expanded to include data from females [15]. Looking at both studies combined, 741 males and 1,000 females (all 20–100 years of age) were chosen to undergo overnight PSG, with oronasal airflow measured using thermocouples. Prior interviews by telephone allowed the researchers to select a stratified random sample, with those exhibiting a greater number of risk factors being over-represented. Using the same scoring rules as the Wisconsin study, a diagnosis of OSAS required an  $\text{AHI} \geq 10/\text{h}$  as well as the presence of adverse daytime symptoms; using these criteria an adjusted prevalence of 1.2% in females and 3.9% in males was found. Using a different set of criteria (an obstructive  $\text{AHI} \geq 15/\text{h}$ ; the mean number of obstructive apnea/hypopnea events per hour of sleep, slightly different from the definition of  $\text{AHI}$ ), 2.2% of females and 7.2% of males were identified as having OSA. Regardless of the diagnostic criteria, then, the Pennsylvania cohort studies found a male:female OSA ratio of 3.3:1.

## *Europe*

A Spanish cohort study published in 2001 used portable, home-based cardio-respiratory monitoring as the basis of selection for laboratory-based PSG, with

oronasal airflow measured using thermistors, for 324 males and 231 females aged 30–70 years [16]. Again, this sample was predominantly Caucasian. Using modified Chicago rules and the same threshold for defining OSAS as the Wisconsin cohort, this study showed the prevalence of OSAS to be roughly similar to that found in North America: 3.0% in females and 3.4% in males. When the criterion for disease was reduced to simply an  $AHI \geq 10/h$  (without daytime hypersomnolence), the prevalence became 14.9% in females and 19.0% in males.

## *Asia*

The first estimates of the prevalence of OSA in Asia were published in 2001 for Chinese males ( $n=150$ ) [17] and 2004 for Chinese females ( $n=106$ ) [18]. Both studies targeted 30- to 60-year-olds through offices and community centers, and all subjects underwent laboratory-based PSG with oronasal airflow measured using thermistors. The same criteria for identifying events as the aforementioned studies were used. It was found that 2.1% of women and 4.1% of men, respectively, had OSAS (an  $AHI \geq 5/h$  in the presence of excessive daytime sleepiness), while 3.7% of women and 8.8% of men had OSA ( $AHI \geq 5/h$ ) alone.

A study of 457 Korean participants aged 40–69 years found that 3.2% of women and 4.5% of men reported excessive daytime sleepiness and exhibited an  $AHI \geq 5/h$  obtained during either a laboratory- or home-based PSG using thermistors. Using the criterion of  $AHI \geq 5/h$  alone, the prevalence increased to 16.8% in women and 27.1% in men [19].

Prevalence statistics based on PSG data from India were made available in 2009 [20]. Males and females aged 30–65 years were recruited and first completed a questionnaire ( $n=2,505$ ), with a subset of these participants undergoing laboratory-based PSG using thermistors for airflow measurement ( $n=365$ ). Using Chicago scoring criteria, an  $AHI \geq 5/h$  in the presence of daytime sleepiness was observed in 1.5% of women and 4.0% of men; an  $AHI \geq 5$  alone was observed in 5.5% of women and 13.5% of men. The prevalence of OSA in Asia is therefore similar across China, Korea and India, and comparable to that seen in other continents.

## *South America*

The first South American study of OSA prevalence was published in 2010, based on PSG data obtained from 1,042 Brazilian participants aged 20–80 years, of both genders [21]. Airflow was measured with both nasal pressure and a thermocouple; the updated AASM rules were used for scoring events, with hypopnea defined according to the alternative criteria. 9.6 and 30.5% of women exhibited an  $AHI \geq 15/h$  and  $AHI \geq 5/h$ , respectively; using the same cut-off thresholds, the prevalence data in men were 24.8 and 46.5%. OSAS was defined as an  $AHI$  of 5–14.9/h in the presence

of loud snoring, daytime sleepiness, fatigue, and/or breathing interruptions, or an  $\text{AHI} \geq 15/\text{h}$  regardless of other symptoms. Using this definition, the prevalence of OSAS was 26.1% in females and 40.6% in males. All of these prevalences are much greater than the figures seen in North America and other parts of the world. The extent to which this difference reflects an increased risk for OSA among Brazilians vs. much more liberal scoring criteria (use of nasal pressure and a 3%  $\text{O}_2$  desaturation threshold to define hypopnea) is unclear.

### *Australasia*

The only prevalence data available from the Australasian population come from two studies utilizing four-channel home-based cardio-respiratory monitoring rather than PSG. In an Australian study of 294 primarily Caucasian males aged 40–65 years, 26% had OSA defined as an  $\text{AHI} \geq 5/\text{h}$ , with a respiratory disturbance defined as an  $\text{O}_2$  desaturation of  $\geq 3\%$  occurring with either an increase in heart rate of  $\geq 10$  beats per minute, and/or snoring at the commencement and termination of the desaturation, while 3.1% had OSAS [22]. A study of 364 New Zealanders (30–59 years old) reported the prevalence of OSAS ( $\text{AHI} \geq 5/\text{h}$  and Epworth Sleepiness Scale [23] score  $\geq 10/24$ ) was 2.0% in Maori females, 0.7% in non-Maori females, 4.4% in Maori males, and 4.1% in non-Maori males [24]. A respiratory disturbance was defined using the same criteria as the Australian study, but used a 4%  $\text{O}_2$  desaturation requirement. When the ethnic groups were combined, 3.4% of females and 12.5% of males had an  $\text{AHI} \geq 5/\text{h}$  alone. Thus, irrespective of definition used, the ratio of male:female prevalence of sleep apnea is roughly 3:1 across continents and ethnic groups.

### **Disease Progression**

Of the prevalence studies using in-laboratory PSG methodology, the Wisconsin sleep cohort provides data as to the progression of OSA as it was performed longitudinally with baseline data collection ( $n=948$ ) followed by 4-year ( $n=690$ ) [13] and 8-year ( $n=282$ ) [25] follow-ups. At baseline, 644 participants were identified with an  $\text{AHI} < 15/\text{h}$  of which 39 (6%) went on to develop moderate-to-severe OSA ( $\text{AHI} \geq 15/\text{h}$ ) over 4 years [13]. Over 8 years, the 282 participants available for follow-up showed an average  $\text{AHI}$  increase of  $2.7 \pm 8.2/\text{h}$  (from  $2.5/\text{h}$  to  $5.1/\text{h}$ ), with men and women having similar average increases ( $3.0 \pm 9.4$  and  $2.3 \pm 6.1/\text{h}$ , respectively) [25]. Of note, there were a greater number of participants whose  $\text{AHI}$  increased than decreased, and many participants with an  $\text{AHI} < 1/\text{h}$  showed an increase to an  $\text{AHI} > 1/\text{h}$  whereas the converse was not true: few participants with an  $\text{AHI} > 1/\text{h}$  showed a decrease to an  $\text{AHI} < 1/\text{h}$ .

Longitudinal data are also available from the Sleep Heart Health Study, a multicentered, community-based cohort study based in the United States using home-based PSGs conducted 5 years apart [26]. Data were available for 1,342 males and 1,626 females aged  $\geq 40$  years at baseline, with snorers oversampled. Approximately 75% of the sample was Caucasian, 13% were Native American, and 6% were African-American. An apnea was defined as a  $\geq 10$ -s reduction in airflow to  $< 25\%$  of baseline, and a hypopnea was defined as a  $\geq 10$ -s reduction in airflow of  $< 70\%$  from baseline, with both measured using a thermocouple and requiring a  $\geq 4\%$   $O_2$  desaturation. The mean AHI increase over 5 years was  $2.2 \pm 9.0$  in females and  $3.4 \pm 12.4$  in males with no differences identified across ethnicities.

Finally, the Cleveland Family Study published in 2003 performed four-channel cardio-respiratory monitoring studies including oronasal airflow measured using thermistors on 486 participants (78% Caucasian, 21% African-American, 2% Hispanic/mixed ethnicity) at baseline and after 5 years [27]. Apneas and hypopneas were scored when a cessation or reduction in airflow was observed accompanied by an  $O_2$  desaturation of  $\geq 2.5\%$ . Over the study period, the median AHI increased from 2.6 to 3.6/h; the prevalence of an  $AHI \geq 15$  increased from 10.5 to 16.3%. Overall, this evidence suggests a slow but steady progression in the AHI over time with rare spontaneous improvements. Much of this deterioration is likely attributable to progressive weight gain (discussed further below).

## Risk Factors

### *Obesity*

The prevalence of obesity in both developed and developing countries has increased markedly over the past few decades [28, 29], and represents a major crisis due to deleterious outcomes including OSA. The high prevalence of obese and morbidly obese patients in clinical OSA populations was recognized early, and there is now a vast amount of evidence from community-based studies supporting this association. In cross-sectional analyses, an increase in body mass index (BMI) of 1 standard deviation ( $5.7 \text{ kg/m}^2$ ) increased the risk of having an  $AHI > 5/h$  by 4.2-fold in the Wisconsin cohort [12], and in the Sleep Heart Health Study a similar increase ( $5.3 \text{ kg/m}^2$ ) was associated with a 1.6-fold increased risk of having an  $AHI \geq 15/h$  [30]. Based on data from the Wisconsin cohort, it has been estimated that 41% of all OSA and 58% of moderate-to-severe OSA can be attributed to excess weight ( $BMI \geq 25 \text{ kg/m}^2$ ) [31]. Epidemiological studies outside the United States have consistently drawn similar conclusions [16–22, 24].

Further evidence comes from longitudinal analyses. The Wisconsin study found that a 10% increase or decrease in weight over 4 years led to a greater than 25% change in AHI in the same direction [13]. In addition, the increase in AHI over 8 years was significantly larger in obese compared with nonobese



individuals [25]. The Sleep Heart Health Study and Cleveland Family Study both reported that an elevated BMI was an independent risk factor for having a greater increase in AHI at follow-up [27, 30]. In an untreated clinical sample, a 2009 study found that the mean change in BMI over 5 years was a strong predictor of having a significant increase in AHI, defined as an increase of more than five events per hour [32].

Moreover, weight loss achieved by surgery [33–35], caloric reduction and/or exercise programs [36–39] can reduce OSA severity, though few of these studies have been of a randomized controlled design. Significant weight loss has not always equated to large AHI reductions as evidenced by the Sleep AHEAD study in which the intervention group lost on average 10.8 kg but experienced a reduction in mean AHI from 22.9/h to only 18.3/h [40]. Data from the Sleep Heart Health Study demonstrate that the increase in AHI associated with a given increase in weight is greater than the decrease in AHI observed with weight loss of the same magnitude [26]. This suggests that weight loss may be more effective as a preventive measure than treatment of established OSA. There is also minimal evidence as to whether the improvement in AHI is sustained once the intervention has been withdrawn [36]. In fact, a number of studies have shown reemergence of OSA following medical or surgical weight loss even without regain of body weight. These data emphasize the need for ongoing clinical follow-up of these patients.

Regardless, the overwhelming evidence from cross-sectional, longitudinal and intervention studies indicates that the association between obesity and OSA is likely to be causative, and there are a number of potential mechanisms. The most obvious of these is a structural change of the pharyngeal airway induced by the accumulation of fat in the upper airway region, leading to increased pharyngeal collapsibility (and critical pressure) [41, 42], and possibly a mechanical decrease in lung volume [43]. A decrease in functional residual capacity may also reduce longitudinal tracheal traction, contributing to upper airway instability [44].

The multifactorial development of OSA as a result of obesity suggests that different measures of body habitus may be more or less useful as predictors of AHI, but this remains a controversial issue. The two main mechanistic proposals mentioned above have led to a focus on neck obesity (affecting the pharyngeal airway) and central obesity (affecting lung volume). Neck circumference, tongue volume, and pharyngeal wall volume are important risk factors of OSA [41, 45], and measures of central obesity such as waist circumference have been shown to be better predictors of OSA than BMI [46]. Furthermore, AHI is more closely correlated with intra-abdominal and subcutaneous abdominal fat measured by magnetic resonance imaging than subcutaneous neck fat or pharyngeal fat [47].

Obesity is generally accepted as the most important predisposing feature for OSA, particularly in Western populations, and because it is one of the only risk factors that is readily reversible and doing so has other significant health advantages, the role of obesity in OSA pathogenesis and its potential role as a target for OSA treatments are areas of research receiving substantial attention.

## ***Age***

The first major community-based study of OSA in older populations ( $\geq 65$  years of age) found that 70% of males and 56% of females had an  $\text{AHI} \geq 10$  detected using four-channel overnight monitoring [48] – markedly more than the prevalences in middle-aged populations discussed above. This greater prevalence has been confirmed in studies using full PSG – in a cohort of 461 females with mean age 83 years, 38% had an  $\text{AHI} \geq 15/\text{h}$  [49], and in a group of 2,849 males with mean age 76 years, 43% had an  $\text{AHI} \geq 15/\text{h}$  [50]. Even within an elderly cohort, the prevalence of OSA appears to increase with age, as evidenced in a study of 2,911 males reporting that 23% of those aged  $\leq 72$  years and 30% of those aged  $\geq 80$  years had an  $\text{AHI} \geq 15/\text{h}$  [51]. In the Spanish cohort, the odds ratio of developing OSA was 2.2 for each decade increase in age [16].

Of course, any nonfatal disease is expected to become more prevalent with age as the number of existing cases accrues. Whether older age is associated with a rise in the incidence rate for OSA is unclear. It has been speculated that an increase in obesity [29], changes in the anatomical structure of the upper airway [52, 53], a decline in neural reflexes [52], or a greater contribution to the AHI from central sleep apnea [14] may account for the increased prevalence of OSA in older populations.

An unanswered question is whether OSA in the elderly, unlike in younger populations, has adverse health consequences. Various cohort studies have found no clinically significant association between OSA severity and sleepiness [49, 54] or reduced neurocognitive capacity [54]. In the Sleep Heart Health Study, OSA was only a risk factor for heart disease in those  $\leq 70$  years of age [55], and there is evidence that moderate OSA may even confer a protective effect on mortality in those  $\geq 80$  years [56]. Other studies, however, have reported contradictory results [51], so the issue as to whether OSA in the elderly represents a separate clinical entity to that seen in the middle-aged remains in dispute.

## ***Gender, Menopause, and Pregnancy***

Male gender is considered to be a risk factor for OSA as every large epidemiological study published to date has found an increased prevalence of OSA in males [12, 14–21, 24], mostly within the range of 2:1–3:1. The gender discrepancy in clinical studies is higher than that seen in community-based studies, indicating that females are under-diagnosed in clinical practice. Clinicians may overlook women with symptoms of OSA simply because they do not fit the picture of a typical patient, and women may be more reluctant than men to report snoring, instead emphasizing other symptoms such as insomnia [57]. There is also some evidence that female bed-partners report a larger decrement in quality of life of their male partner with OSA than vice versa [58], which may prompt a higher number of referrals for male patients initiated by their partners. Despite this, it has been reported that female

OSA patients use healthcare resources significantly more than severity-matched men, possibly due to lower perceived health status [59].

Several studies have investigated the effects of gender further by incorporating menopausal status. Menopause was a significant risk factor for having an  $AHI \geq 5/h$  and  $\geq 15/h$  after controlling for age, obesity, presence of cardiovascular disease, and alcohol/cigarette consumption in the Wisconsin cohort [60]. In the Pennsylvania cohort, postmenopausal women had a significantly higher prevalence of OSA than premenopausal women (1.9 and 0.6%, respectively) [15]. Postmenopausal women receiving hormone replacement therapy have similar prevalence rates to premenopausal women [15], and lower prevalence rates than postmenopausal women not receiving hormones [61]. Considered alongside the evidence that the prevalence of OSA is similar between males and females in the pediatric population, and between postmenopausal women not receiving hormone replacement therapy and adult males [15], these data suggest that there may be a protective effect of estrogen and/or progesterone in women of reproductive age relating to the enhancement of ventilatory control [62, 63]. Administration of estrogen to postmenopausal women can significantly lower the AHI [64, 65], but only one of these studies found a further benefit after additional administration of progesterone [65]. However, the effect of hormone replacement therapy on cancer and cardiovascular risk does not support its routine use for OSA.

Pregnancy appears to induce snoring and symptoms indicative of OSA [66–69], occurring to a greater extent in women experiencing large increases in neck circumference [69]. Pregnant women have smaller upper airway diameters compared with nonpregnant women, and experience a significant increase in upper airway size following childbirth [68]. Snoring and witnessed apnea are closely associated with hypertension during pregnancy after controlling for a number of known confounders [70] and may also lead to deleterious outcomes for the fetus [67, 71], emphasizing the need to closely monitor pregnant women for the development of OSA, particularly those who were obese pre-pregnancy [72].

Apart from hormonal influences, the major factors accounting for the gender difference in OSA are probably related to differences in craniofacial structure [73–75], upper airway length [76, 77], and body habitus.

## ***Craniofacial Features***

The pharyngeal airway – the segment comprised of the nasopharynx, velopharynx, oropharynx, and hypopharynx – is a skeletal enclosure containing various soft tissues responsible for multiple functions including swallowing, speech, and breathing. Both the size and position of the bony structures and soft tissues can influence upper airway size and the propensity for collapse. In addition, pharyngeal airway length is important as a longer airway is more collapsible than a shorter one [76, 78].

Soft tissues of the upper airway include the pharyngeal muscles, tongue, uvula, tonsils, soft palate, pharyngeal fat pads, and lateral pharyngeal walls.

Abnormal enlargement of any of these tissues through hypertrophy, inflammation, or edema will produce a narrowing of the lumen. It has recently been highlighted that the volume of upper airway soft tissue proportional to the cross-sectional craniofacial area should be considered in assessing OSA risk [79]. A simpler approach for risk stratification that can be readily utilized in the clinical setting is use of the Mallampati score. This grading of oropharyngeal crowding is predictive of OSA severity independent of overall neck circumference [80].

Skeletal structures of the pharyngeal airway include the nasal concha, maxilla and mandible, hyoid, and the cervical vertebrae. Abnormal positioning of these bones, primarily maxillomandibular retropositioning and inferior placement of the hyoid, will encroach on the space available for the lumen regardless of the size and position of soft tissues. Retrognathia assessed by cephalometry has been shown to occur in OSA patients to a greater extent than controls [81]. Similarly, a more collapsible airway measured by endoscopy is associated with a smaller maxilla and mandible [42]. The ratio of maxilla to mandible size and maxilla to facial width may also be important [82].

In humans, the hyoid is free-floating to allow speech, rather than being attached to the cervical spine. This makes the upper airway less rigid than that seen in other mammals and therefore more susceptible to collapse, particularly with the additional force of gravity while in the supine position. Many have suggested that this could be one reason why OSA is an almost exclusively human condition [83]. The distance from the posterior nasal space to the hyoid correlates positively with pharyngeal collapsibility [84], and lower placement of the hyoid may potentially predict AHI [85].

Although craniofacial abnormalities can sometimes be subtle and therefore difficult to detect in the usual clinical setting, it is possible that craniofacial phenotyping through photographic analysis [86, 87] or imaging techniques [88] could be used to predict accurately the presence of OSA and/or a positive response to treatment by mandibular advancement [89].

## ***Ethnicity***

As mentioned, the major OSA prevalence studies from the United States [12, 14, 15], Europe [16] and Australia [22] have recruited predominantly Caucasian samples, making the worldwide distribution of OSA and any ethnic disparities difficult to elucidate. What data do exist suggest that the prevalence of OSA in Asian populations is similar to that in United States and European Caucasians [17–20], although at a lower level of obesity.

Because obesity tends to be more prevalent in minority groups, OSA may be expected to be more common amongst these groups. This appears to be the case in relation to Native Americans in the United States. In the Sleep Heart Health Study, Native Americans were 70% more likely than Caucasians to have an AHI > 15/h, but this difference disappeared after adjustment for differences in obesity [30].

Similarly, in a New Zealand study, those of Maori heritage were 4.3 times more likely to have an  $AHI \geq 15$  than non-Maori, but once BMI was controlled for ethnicity was no longer an independent risk factor [24]. A number of studies have examined whether independent of obesity, African-Americans may be at elevated risk for OSA compared to Caucasians. While studies suggest that both young and elderly African-Americans may be at greater risk [90, 91], no increased risk has been identified in middle-aged individuals [30].

In contrast, a wealth of data suggests that for the same level of obesity, Asians are at greater risk of OSA than other groups. For example, while OSA prevalence is similar in China [17, 18], Korea [19] and India [20] to that seen in the United States [12, 14, 15], the mean BMI is substantially greater in U.S. cohorts. In addition, Asian subjects may present with more severe disease [92]. Given the lower prevalence of obesity throughout Asia, it is likely that risk factors for OSA other than obesity are particularly common among Asians. Asians appear to have a significantly more crowded oropharynx, and significantly shorter thyromental distance than Caucasians [93]. Similarly, another study found that Chinese participants had a higher degree of bony restriction as measured by cephalometry than Caucasians [94]. Craniofacial differences have been shown to exist within the Asian community (comparing Malay, Indian, and Chinese subjects [95]), indicating that different anatomical measurements may be more relevant in some groups than others. Similarly, despite having similar overall risks for OSA, comparative data suggest the relevant craniofacial risk factors for OSA likely differ in Maori and African-Americans compared to Caucasians [96–98].

## *Alcohol and Cigarette Consumption*

Regular intake of both alcohol and cigarettes have been associated with snoring and/or OSA in univariate analyses of some [19, 20, 22, 24] but not all [17] observational studies, which have relied on subjective reporting of consumption.

Only one study has reported that habitual alcohol consumption in males is associated with an increased risk of OSA after adjustment for age, measures of body habitus, smoking and medication use, but no association was found in females [99]. Randomized studies indicate that moderate alcohol consumption can significantly increase the AHI in snoring volunteers [100] and the  $O_2$  desaturation index in patients with established OSA [101]. Possible mechanisms for this effect include the reduction of respiratory motor control and/or a blunted chemoreceptor-initiated response to hypoxia.

Habitual snoring is significantly more prevalent in current-, ex- and even passive-smokers compared with never-smokers, after controlling for age, gender and BMI [102]. Data collected from a registry of male twins indicate that this association may not hold for more clinically significant OSA [103], although cessation is still recommended given the recent emergence of evidence that smokers with OSA are at a higher risk of cardiovascular complications than controls matched for age,

gender, BMI, OSA severity and presence of cardiovascular disease [104]. It is possible that cigarette smoking may cause snoring due to inflammation of the upper airway, but at this stage the mechanistic evidence is weak and should be a focus of future research.

### ***Familial/Genetic Factors***

OSA clearly runs in families. Compared to an individual with no relatives with OSA, having one relative with OSA increases one's own risk of disease 1.6-fold [105]. The risk further increases with a greater number of affected relatives – the risk is 2.5-fold greater if one has two relatives with OSA and 4.0-fold greater if one has three relatives with OSA. The heritability of the AHI has been found to be 30–35% in several studies suggesting one-third of the variability in this measure is explained by shared familial factors [106–108]. Many of the risk factors for OSA including obesity and craniofacial shape are known to have a genetic basis and this may explain the familial nature of OSA. About 40% of the total genetic variance in the AHI is explained by obesity [109] leaving the majority of the genetic basis for OSA explained by obesity-independent factors such as alterations in ventilatory control. In support of this notion, individuals with OSA are more likely to have a child with sudden infant death syndrome (SIDS), a disease characterized by reduced ventilatory drive [110, 111].

Genetic studies have suggested that OSA is a complex disease with multiple susceptibility genes each with small to moderate effect [106, 107]. Although numerous polymorphisms have been reported in the literature to predict OSA, these findings have been inconsistent. To date, no polymorphism has been definitively identified as a risk factor for OSA.

### **Summary of Keypoints**

- There is an absence of international agreement as to how to define obstructive respiratory events, and what should constitute a clinical diagnosis of OSA.
- The most widely cited prevalence study from the Wisconsin Sleep Cohort found that 24% of middle-aged males and 9% of middle-aged females have OSA based on an AHI  $\geq 5$  events/h with or without daytime symptoms.
- Longitudinal studies suggest a slow but steady increase in disease severity over time, particularly in association with weight gain, with rare spontaneous improvements.
- Obesity has been consistently identified as the most important reversible risk factor for OSA, with evidence from cross-sectional, longitudinal and interventional studies suggesting a causative link.
- The gender discrepancy in clinical studies is higher than that seen in community-based studies, indicating that females are under-diagnosed in clinical practice potentially due to referral bias or gender differences in symptoms.

- Both the size and position of the pharyngeal bony structures and soft tissues can influence upper airway size and the propensity for collapse.
- Most ethnic differences in OSA prevalence can be explained by obesity. However, prevalence rates in Asia are similar to those in North America and Europe but at a lower level of obesity, suggesting additional risk factors in Asian groups.
- Genetic studies have suggested that one-third of the variability in OSA severity can be explained by shared familial factors.

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# Chapter 6

## Obstructive Sleep Apnea: Clinical Features and Adverse Consequences

Geraldo Lorenzi-Filho and Pedro Rodrigues Genta

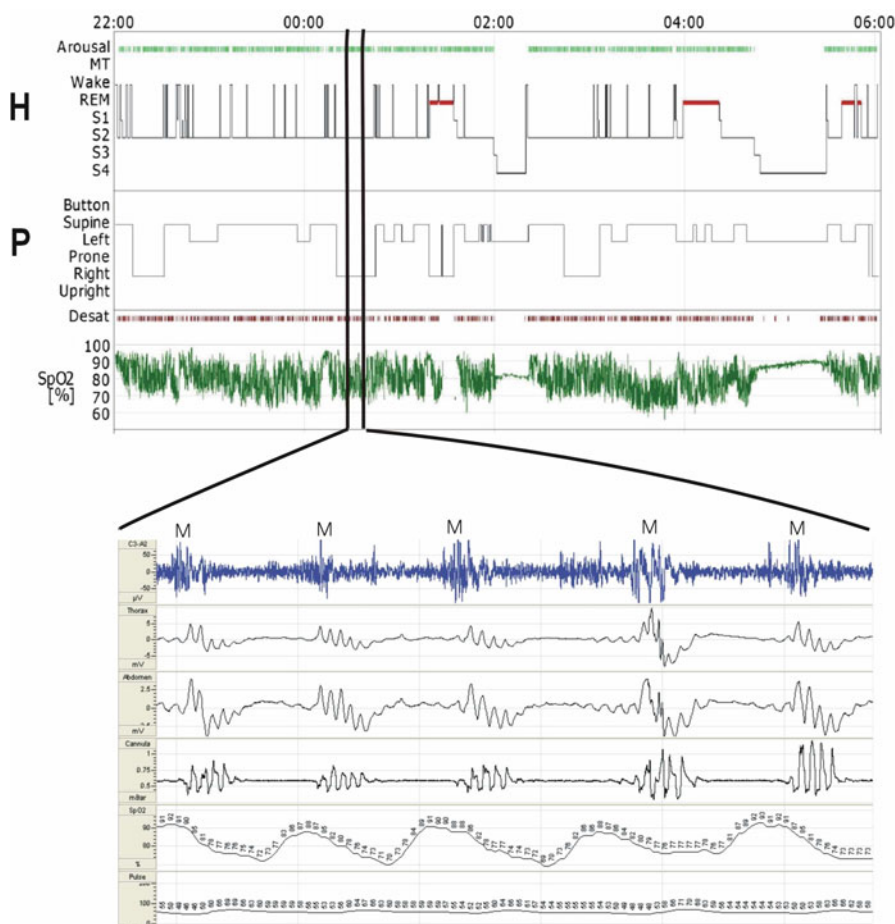
**Keywords** Obstructive sleep apnea • Clinical features • Signs • Symptoms • Cardiovascular consequences • Metabolic disorders

### Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by repetitive episodes of partial or total upper airway obstruction during sleep resulting in hypopneas or apneas, respectively. The episodes of upper airway obstruction result in exaggerated intrathoracic pressure swings, asphyxia (characterized by hypoxemia and hypercapnia), and fragmented sleep. The typical signs of OSA include loud and irregular snoring and disturbed sleep due to the multiple arousals and awakenings. The typical patient with OSA complains of nonrestorative sleep and daytime tiredness and/or excessive sleepiness. However, a large number of patients may deny or actually not have typical symptoms. There is growing recognition that OSA is tightly associated and may contribute to several cardiovascular diseases, including hypertension and atrial fibrillation. OSA syndrome is a denomination reserved for patients that present with OSA plus associated symptoms, including sleepiness and/or cardiovascular disease. The repetitive episodes of apneas or hypopneas represent a stress that can result or contribute to cardiovascular and metabolic diseases. It is now recognized that severe OSA is independently associated with poor cardiovascular outcome, including myocardial infarction, stroke, and death from cardiovascular cause.

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**Fig. 6.1** Polysomnography report of a patient with severe obstructive sleep apnea (apnea–hypopnea index = 87 events/h). **(H)** Hypnogram showing a fragmented sleep with multiple awakenings and arousals; **(P)** body position; **(SpO<sub>2</sub>)** oxygen saturation. The figure in the bottom part shows a 3-min recording of a few channels: EEG (C3–A2), respiratory monitoring by thorax and abdomen belts, nasal cannula, oximetry and pulse derived from oximetry. The patient is presenting with multiple obstructive events characterized by absence of airflow (nasal cannula) with continued effort to breathe depicted by the movements in thoracic and abdominal belts. Observe the profound oxygen desaturations associated with the obstructive events. The delay between the end of the respiratory event and the nadir in oxygen saturation is due to circulatory delay (SpO<sub>2</sub> was measured at the finger tip) and the delay in oximeter signal

Overnight full polysomnography (PSG) is considered the gold standard method for diagnosis and classification of OSA severity. The PSG of a patient demonstrating repetitive episodes of apneas is presented in Fig. 6.1. The primary consequences of OSA include: (1) Recurrent episodes of asphyxia (hypoxemia + hypercapnia); (2) Exaggerated negative intrathoracic pressure; (3) Arousals from sleep resulting

in fragmented sleep. These respiratory events (i.e., apneas or hypopneas) may impact on the macro structure of sleep, resulting in loss of restorative sleep, including slow wave and rapid eye movement (REM) sleep. The main metric derived from PSG is the number of apneas+hypopneas/h of sleep (AHI). AHI<5 events/h is considered normal, while AHI 5–15, 16–30 and >30 events/h is consistent with mild, moderate and severe OSA, respectively.

## **Risk Factors for OSA**

Because some patients may not readily report their symptoms or be minimally symptomatic, OSA is frequently under-recognized in clinical practice. Therefore, it is important to determine which groups of patients are at increased risk for OSA. The risk factors for OSA are to some extent linked to the pathophysiology of OSA. While awake, dilator muscles stiffen and dilate various regions of the upper airway, keeping it patent. Their activity is reduced during sleep, leading to narrowing of the upper airway. In addition to the upper airway dilator muscle activity during sleep, a number of factors are known to contribute to the pathogenesis of OSA, including, upper airway anatomy, lung volume, ventilatory control stability, sleep state stability, and rostral fluid shifts. The relative contributions of each factor may vary between individuals. The main risk factors associated with OSA are listed below.

### ***Obesity***

Increased soft tissue, as is found in obesity, is the main factor for reduced upper airway lumen and OSA. Obesity is postulated to cause OSA via mechanical effects on airway size. In addition, obesity may also affect upper airway patency indirectly through changes in lung volume and neural effects that blunt the neuromuscular response. Lower end-expiratory lung volume, as occurs in the setting of obesity, increases the tendency of the upper airway to collapse. This effect is thought to be mediated by the decreased “tug” of the trachea, which stiffens and dilates the upper airway as lung volumes increase. Independent of the exact mechanism, obesity is a strong risk factor for OSA. Among patients with OSA, 70% are overweight or obese. In the Sleep Heart Health Study the prevalence of moderate to severe OSA was threefold higher in the highest quartile of body mass index (BMI), relative to the lowest. In clinical practice, a BMI>30 kg/m<sup>2</sup> should be regarded as a risk factor for OSA. For instance, approximately 30% of patients with a BMI greater than 30 kg/m<sup>2</sup> have OSA and 50% of patients with a BMI greater than 40 kg/m<sup>2</sup> have OSA. Therefore, independent of the reasons for clinical evaluations, obese patients should be carefully evaluated for other traits and symptoms suggestive of OSA.

## *Age*

The prevalence of OSA has been shown to increase with age in adults, up to age 65. This age-related increase has been attributed to parapharyngeal fat deposition, soft palate-lengthening, and changes in other parapharyngeal structures. Some authors have suggested that the clinical presentation of OSA in the elderly is different and that the cardiovascular consequences may be less severe. In the Sleep Heart Health Study, sleep disordered breathing in older people was poorly predicted by obesity, neck circumference, and self-reported apneas.

## *Sex*

OSA is more common in males than in females. The male predominance in OSA prevalence is related to sex-related differences in upper airway anatomy and function, obesity and fat distribution, ventilatory control, and hormonal status. Most population-based studies have found a two to threefold higher prevalence of OSA in males than in females. The ratio of men to women diagnosed in sleep centers is even more skewed toward men, with reported ratios of 8:1 and higher. There is therefore a tendency to under-diagnose women in clinical practice. Women may present with less severe OSA, report nonspecific symptoms more frequently which may lead clinicians to consider other diagnoses. Among males, the most important risk factor for OSA is obesity. In contrast, women are relatively protected from severe OSA. After menopause, the prevalence of OSA rises dramatically. Therefore, among women, the most important risk factor for severe OSA is age. Women frequently present with “atypical” symptoms, and do not complain of EDS, but of tiredness, lack of energy, and symptoms that overlap with depression.

## *Ethnicity*

Some ethnic groups may be at greater risk for OSA. For example, African-Americans present a higher risk for OSA than Caucasians. Recent studies have suggested greater severity of OSA among Asians as compared to Caucasians controlled for BMI. Conversely, Asians are leaner than Caucasians when AHI is paired. Taken together, these data suggest that Asians are predisposed to developing OSA. Differences in craniofacial anatomy have been proposed to explain this apparent propensity to OSA among Asians as compared to Caucasians. One alternative explanation is that the comparison of BMI among Asians and Caucasians is misleading and does not capture differences in body composition. Asians have more body fat at lower BMI than Caucasians. The World Health Organization recognizes these differences and proposes different BMI cut-offs to define obesity according to ethnic group. A BMI  $\geq 25$  kg/m<sup>2</sup> should be used to define obesity in Asian populations, which contrasts with the definition for all other groups (BMI  $\geq 30$  kg/m<sup>2</sup>). Therefore, a higher fat deposition for



any BMI helps to explain why OSA is common in apparently lean Asians. Supporting this hypothesis, epidemiological studies showed a similar prevalence of OSA in Asian populations and Americans. In clinical practice, one must have in mind that a lower BMI threshold ( $\text{BMI} > 25 \text{ kg/m}^2$ ) should be used as the cut-off for defining obesity among Asians.

### ***Bony Structures***

The bony enclosure (skull) interacts with soft tissue structures to determine upper airway collapsibility. A small maxilla and mandible are extremely important and will be addressed later on in this chapter in the topic “physical examination.” Although obesity is one of the main risk factors for OSA, OSA is extremely common and many patients with OSA are actually lean. In this group of patients, subtle alterations in bony structure, such as a small mandible or arched palate frequently is present and helps to explain the small airways and propensity to collapse during sleep.

### ***Diseases Associated with Edematous States***

Fluid shifts from the legs to the neck appear to play a role in the pathogenesis of OSA. Fluid displacement from the legs caused by lower body positive pressure has been shown to reduce upper airway size and increase collapsibility in healthy awake subjects. Further, overnight rostral fluid displacement from the legs was found to be correlated strongly with AHI, change in neck circumference, and time spent sitting, in nonobese, healthy men suspected of having OSA. This mechanism may explain the finding that lack of exercise is associated with increased severity of sleep disordered breathing, independent of measures of body habitus. Greater time spent in sedentary activity may increase lower leg edema and result in more sleep-related fluid shift to the upper airway. From the clinical point of view the most important message is that patients with diseases that may trigger edematous states, such as renal failure and congestive heart failure are at increased risk of OSA at a lower BMI. Despite being lean, the prevalence of OSA among patients with chronic renal failure under dialysis and in patients with congestive heart failure is strikingly high. Patients with congestive heart failure are at increased risk of both central sleep apnea associated with Cheyne–Stokes respiration as well as OSA. The reasons for central sleep apnea in patients with congestive heart failure are beyond the scope of this chapter.

### ***Positive Family History***

Relatives of patients with OSA have a two to fourfold increased risk of OSA compared with control subjects. The reason for this aggregation is multiple and includes

inherited craniofacial characteristics, propensity to obesity, and probably other factors such as control of ventilation, regulation of inflammation and upper airway muscle control. Several candidate genes that may help to explain the propensity to OSA are under investigation. From the practical point of view, first relatives of a patient recently diagnosed with OSA must be advised of the increased risk of having the disease. Conversely, patients seeking medical attention should be asked if they have relatives with OSA.

### ***Hypothyroidism***

OSA is more prevalent among patients with hypothyroidism. Hypothyroidism leads to the accumulation of hyaluronic acid in the skin and subcutaneous tissue that provokes the enlargement of tongue and pharyngeal mucosa. In addition, hypothyroidism may lead to a decrease in central ventilatory drive.

### ***Presence of Co-Morbid Conditions***

OSA is tightly linked to several cardiovascular and metabolic diseases, including hypertension, atrial fibrillation, diabetes, stroke, congestive heart failure, and metabolic syndrome. These conditions will be discussed in the last part of this chapter (consequences of OSA). It is important to note that the prevalence of OSA among these patients is much higher than in the general population. Moreover, several of these patients do not report typical symptoms. Therefore, having one of these conditions is a risk factor for OSA.

### **Clinical Symptoms**

Patients with OSA frequently do not report their symptoms. The main reason is that the patient is not aware of what is happening to him/her during sleep. In addition, patients with OSA may not perceive themselves as being “sleepy.” Therefore, a careful interview as well as collateral information from a bed partner is extremely important. The symptoms associated with OSA may be divided in night, morning, and daytime (Table 6.1). The overnight symptoms include frequent, loud, disturbing, and irregular snoring. Witnessed apneas are the most specific symptoms associated with OSA. It is remarkable that most patients are not aware of their sleep problems. Several patients rate themselves as “good sleepers.” A subgroup of patients with OSA may complain of insomnia with difficulties in initiating and maintaining sleep. Insomnia is more common in women and in patients with mild to moderate forms of OSA.

**Table 6.1** Symptoms associated with OSA

Period	Symptom	Comments
S	Loud snoring	Less specific is elderly population
L	Witnessed apneas	One of the most specific symptoms, overlaps with central apnea
E	Choking	Overlaps with laryngospasm
P	Dry mouth	Unspecific
	Nocturia	Unspecific
	Restless sleep	Patients are frequently not aware
	Insomnia	More common in mild OSA
M O R N I N G	Nonrefreshing sleep	Commonly reported
	Headache	Unspecific
D	Sleepiness	Frequent in patients referred to sleep clinics
A	Tiredness	Frequent among women <sup>a</sup>
Y	Memory loss	Unspecific
	Sexual impairment	Frequently not reported

<sup>a</sup> Women more frequently complain of unspecific symptoms such as fatigue, irritability, decreased energy, headaches, chronic muscle pain, and other depressive symptoms

Patients typically complain of daytime somnolence with drowsiness, particularly during “passive situations” such as after meals, while watching television, or attending a lecture. The hallmark daytime symptom of OSA is excessive daytime sleepiness (EDS). EDS is thought to be related to the fragmented and nonrestorative sleep. The most popular form to assess EDS is through the Epworth Sleepiness Scale. This is a self-administered scale in which the patient rates his/her probability of doze off (0–3) in eight different situations typical of daily life (Fig. 6.2). The scale therefore may vary from 0 to 24 and scores > 10 are compatible with EDS. Patients with OSA may not complain of EDS but may report tiredness. Fatigue, irritability, decreased energy, headaches, chronic muscle pain, and other depressive symptoms are more common in women. However, several patients with OSA are minimally symptomatic and may deny or report no symptoms. In this group of minimally symptomatic patients treatment may be justified on the basis of prevention of the cardiovascular, metabolic consequences of OSA.

**Physical Signs**

The most common physical sign associated with OSA is obesity, as characterized by a BMI > 30 kg/m<sup>2</sup> in Caucasians and BMI > 25 kg/m<sup>2</sup> in Asians. Central obesity is a more specific risk factor for OSA, and can be measured in clinical practice by neck and waist circumferences. The cut-off points for large neck circumference most used are > 17 in. (43 cm) and 16 in. (41 cm) in males and females, respectively.

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

Situation	Chance of dozing			
	0	1	2	3
Sitting and reading				
Watching TV				
Sitting inactive in a public place (e.g a theater or a meeting)				
As a passenger in a car for an hour without a break				
Lying down to rest in the afternoon when circumstances permit				
Sitting and talking to someone				
Sitting quietly after a lunch without alcohol				
In a car, while stopped for a few minutes in traffic				

0 = no chance of dozing  
1 = slight chance of dozing  
2 = moderate chance of dozing  
3 = high chance of dozing

**Fig. 6.2** Epworth sleepiness scale

Large waist circumference should be considered as the same as that used for metabolic syndrome >40 in. (102 cm) and >35 in. (88 cm) in males and females, respectively. Among Asians these cut-off points are reduced to 35 in. (88 cm) and 31 in. (79 cm) in males and females, respectively.

Overweight and obesity are present in approximately 70% of the patients with OSA. However, because OSA is very common in the general population, a large number of patients with OSA have normal weight. As stated earlier, only 50% of patients with a BMI >40 kg/m<sup>2</sup> have OSA, clearly indicating that other factors play a role in the genesis of OSA. The other physical signs associated with OSA are directly related to upper airway anatomy and must be carefully evaluated. A crowded pharynx is one of the most common physical signs associated with OSA. It can be assessed by the modified Mallampati score proposed by Friedman. The other physical signs associated with OSA include lateral narrowing of the posterior pharynx, enlargement of the uvula, tongue and tonsils. Other physical signs that may also help to recognize patients at high risk for OSA include retrognathia, overjet, and arched palate.

## **Adverse Consequences of OSA**

### ***Consequences Directly Linked to Symptoms***

The symptoms that frequently are the motive for patients with OSA to seek medical attention are thought to be directly linked to the adverse consequences of OSA. However, patients with OSA frequently have overlapping diseases that may explain, at least in part some of the symptoms attributable to OSA. The best way to prove a direct cause and effect relationship between OSA and an adverse consequence is to observe the effects of the treatment OSA on a particular symptom. EDS, daytime tiredness or fatigue is a common complaint of patients with OSA referred to sleep centers. These symptoms are frequently dramatically improved after initiation of treatment of OSA with CPAP. Drivers with OSA are at increased risk of motor vehicle crash. Daytime sleepiness improves significantly following a single night of OSA treatment with CPAP, and simulated driving performance improves significantly within 2–7 days of treatment. Several studies have consistently shown that there is a significant crash risk reduction following treatment of OSA with CPAP. Cognitive impairment, including attention deficit, memory decline, and impaired concentration and judgment has been associated with OSA. However, the reversion of these symptoms with CPAP is less clear than the reversion of EDS. This does not prove that OSA did not cause the disease. Central nervous system alterations caused by OSA may be irreversible at the time of the diagnosis and treatment initiation. The most likely explanation is that OSA causes microvasculature alterations in the central nervous system and therefore not reversible changes. This mechanism may also help explain the presence of residual EDS in several patients with OSA after effective treatment with CPAP.

### ***Cardiovascular and Metabolic Consequences***

The prevalence of cardiovascular disease among patients with OSA is extremely high. Conversely, among patients with established cardiovascular disease the prevalence of OSA is much higher than in the general population and is estimated to be ~30% among patients with hypertension, ~70% among patients with resistant hypertension, ~50% among patients with atrial fibrillation, ~30% in patients with coronary artery disease, and ~50% among patients with type 2 diabetes. One plausible explanation is based on the fact that OSA and all above-mentioned cardiovascular diseases share several risk factors including obesity, male sex, increasing age, and sedentary lifestyle. In addition to this explanation, there is good evidence that OSA may contribute to cardiovascular and metabolic deregulation. The pathways triggered by OSA that are potentially harmful to the cardiovascular and metabolic system are multiple and include increased sympathetic activity, oscillations in blood pressure, oxidative stress,

systemic inflammation, insulin resistance, dyslipidemia, and endothelial dysfunction. Patients with OSA may have activation of neutrophils and monocytes with increased production of reactive oxygen species, and expression of adhesion molecules and enhanced cytokines production, including interleukin 6 and tumor necrosis factor alpha. Many study, although not all, have shown that patients with OSA have elevated C-reactive protein levels that may be attenuated with the treatment with CPAP. There is increasing evidence that OSA may contribute to acceleration of atherosclerosis, and that the treatment of OSA can revert this process. The activation of these pathways may contribute to the development and aggravation of hypertension, heart remodeling, atrial fibrillation, and diabetes. Patients with OSA are at increased risk for development of heart failure, future myocardial infarction, stroke, and death from cardiovascular disease. Distinct cohort drawn from patients referred to a sleep laboratory in Spain, from the general population in Wisconsin, Busselton (Australia), and the Sleep Heart Healthy Study showed consistently that severe OSA is independently associated with risk of future cardiovascular death, mainly due to stroke and coronary artery disease. The treatment of OSA with CPAP is also associated with a reduction in cardiovascular mortality. However, these are observational studies and future randomized studies are necessary to fully elucidate if the treatment of OSA with CPAP is able to reduce cardiovascular mortality. One relevant clinical aspect is that, in contrast to patients referred to sleep laboratories, cross-sectional studies in patients with established cardiovascular disease have consistently shown that these patients are frequently minimally symptomatic. This observation further increases the importance of answering the question whether the treatment of OSA will decrease future cardiovascular events in this group of patients.

## ***Hypertension***

Hypertension is the most studied and well documented link between OSA and cardiovascular disease. Patients with OSA experience oscillations in blood pressure that occur in concert with respiratory oscillations with peaks in blood pressure that occur a few seconds after the termination of each respiratory event. These oscillations occur in association with profound oscillations in sympathetic activity that peaks just before the termination of each respiratory event. Patients with OSA tend to lack the sleep-related nocturnal decrease in blood pressure (nondippers), present with masked hypertension or overt hypertension. In addition to sympathetic overactivity several other interrelated mechanisms may contribute to hypertension in patients with OSA and include chemoreceptor stimulation, decreased baroreflex sensitivity, activation of renin-angiotensin system, systemic inflammation, and endothelial dysfunction.

OSA and hypertension are tightly linked, making it difficult to prove a cause and effect relationship in cross-sectional studies. OSA was independently associated with an increased risk of developing future hypertension in both the Wisconsin cohort study and the Sleep Heart Health Study. Several studies have shown a fall in blood pressure after the treatment of OSA with CPAP. However, the magnitude of

the blood pressure fall is quite variable between studies. There are studies that demonstrated that CPAP lowers blood pressure solely in patients with OSA plus daytime sleepiness, but not in those with mild apnea or even severe disease with only minimal clinical symptoms. The hypothesis that the effects on blood pressure are nonexistent in patients without EDS has not been replicated in one large study. However, when all studies are pooled together the overall fall in blood pressure after CPAP is relatively small (~2 mmHg) and seems to be more pronounced in patients with severe OSA and in patients with high and uncontrolled blood pressure at study entry. There is also some evidence that the prevalence and effects of treatment on blood pressure may be more evident among patients with resistant hypertension. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recognizes OSA as an identifiable cause of hypertension.

### ***Coronary Artery Disease***

In the general population, the risk of developing acute coronary disease increases in the first morning hours and is coincidental with a peak in the sympathetic activity. In contrast, there is some evidence that OSA may predispose to nocturnal angina that can be reverted with the treatment with CPAP. There is some evidence that among patients with coronary artery disease, patients with OSA have more severe coronary atherosclerotic disease than patients without OSA. There is also some evidence that OSA is independently associated with subclinical coronary artery disease. In the Sleep Heart Health Study, it was shown that OSA was an independent risk factor for coronary artery disease. One observational study showed that patients with OSA and coronary artery disease had lower mortality when OSA was treated as compared to those not treated for OSA.

### ***Stroke***

Sleep-related breathing disorders are both a possible risk factor and a consequence of stroke. Sleep apnea is very common following stroke (60–70%) and may in part be a consequence of instability of respiratory drive to breath and central apneas. There are several mechanisms by which OSA may contribute to increased risk of stroke such as: hypertension, oscillations in blood pressure during respiratory events with cyclic episodes of decreased cerebral blood flow, atherosclerosis progression, increased platelet activity, and hypercoagulability. Observational cohort study which followed patients who were referred for a sleep study found an increased risk of stroke or death among patients with OSA. Prospective cohort studies have shown that OSA is associated with increased risk of stroke. Similarly to what has been previously described, patients with stroke frequently do not have the typical OSA symptoms.

## ***Arrhythmias***

Patients with OSA experience cyclic oscillations in heart rate, with progressive bradycardia during apneas, followed by tachycardia that occurs in concert with ventilation. The heart rate oscillations reflect autonomic instability and do not represent a threat to the patient. Frequent ventricular ectopic beats, atrio-ventricular blockade are more frequent in patients with OSA than in controls. Among patients with heart failure and implantable cardioverter-defibrillator, the frequency of life-threatening ventricular arrhythmia was higher among patients with sleep disordered breathing and was more likely to occur during sleep. In another study, people with OSA had a peak in sudden death from cardiac causes during the sleeping hours, which contrasted strikingly with people without OSA that presented a peak of sudden death from cardiac causes during the morning period. This study however did not investigate the cause of sudden death and only reported on the timing of sudden death, therefore not implying that OSA is associated with increased events.

The most relevant arrhythmia associated with OSA is atrial fibrillation. There are several pathways that may help to explain the link between OSA and atrial fibrillation and include heightened sympathetic neural activity, instability in autonomic tone, and systemic inflammation. In addition, the thin-walled atria may be most vulnerable to increased transmural forces experienced during obstructive events. The stressed atria over time could contribute to chamber enlargement, a risk factor for atrial fibrillation. Cross-sectional echocardiographic studies have consistently shown that patients with OSA have higher left atrial volume indices than BMI-matched controls without OSA.

Patients with atrial fibrillation have a high prevalence of OSA. In one study, the recurrence of AF 1 year after electrical cardioversion occurred significantly less in patients with OSA effectively treated with CPAP than in patients with OSA that were not treated (42 vs. 82%). These data therefore, although not definitive, suggest that OSA contributes to the genesis of atrial fibrillation and that the treatment of OSA with CPAP may reduce the incidence of atrial fibrillation.

## ***Diabetes and Metabolic Syndrome***

According to the National Cholesterol Education Program–Adult Treatment Panel (ATP III) metabolic syndrome is based on simple clinical findings that include abdominal obesity, dyslipidemia, hypertension, and increased plasma glucose. According to clinical and epidemiological studies, the cluster of risk factors known as the metabolic syndrome is associated with increased risk for cardiovascular events and mortality in the general population. The prevalence of OSA among patients with metabolic syndrome is strikingly high (~70%) and because OSA interacts and may aggravate all components of metabolic syndrome, it should be incorporated as part of the syndrome. The Sleep Heart Health Study showed that sleep-related hypoxemia was associated with glucose intolerance independently of



age, sex, BMI, and waist circumference. OSA severity was also associated with the degree of insulin resistance after adjustment for obesity. The Wisconsin Sleep Study demonstrated a significant cross-sectional association between OSA and type 2 diabetes for all degrees of OSA, which persisted for moderate-to-severe OSA after adjustment for obesity. Despite the strong evidence indicating that OSA and type 2 diabetes are associated, the studies supporting a putative role for OSA in the development of type 2 diabetes are limited. Moreover, some authors have proposed a reverse direction of causality since autonomic neuropathy caused by diabetes could generate disturbed control of respiration. The effects of CPAP treatment on glucose metabolism have been evaluated in both nondiabetic and diabetic patients, with controversial results. While some studies showed an improvement in insulin resistance, others failed to show any significant effect. In type 2 diabetic patients with OSAS, observational studies using continuous glucose monitoring techniques have reported positive effects of CPAP on glycemic control. Another study showed that postprandial glucose values were significantly reduced 1 h after treatment, and HbA1c level decreased in patients with abnormally high baseline HbA1c. A retrospective study also confirmed a slight reduction in HbA1c in diabetic patients with OSA treated with CPAP. However, a randomized controlled trial comparing therapeutic or placebo CPAP for 3 months found no difference in terms of glycemic control or IR in these patients. In summary, the impact of obesity may offset the impact of CPAP in patients with type 2 diabetes. Similarly, the effects of CPAP treatment on the MetS are controversial. It is possible that OSA treatment may positively affect only some components of metabolic syndrome (such as blood pressure) rather than affecting all of them.

## Conclusion

OSA is extremely common in the general population and even more common among specific populations of patients with high cardiovascular risk. The typical patient with OSA is an obese, middle age male with loud snoring and excessive daytime sleepiness. However, there is growing awareness that these several patients are not obese or are minimally symptomatic. Women frequently complain of nonspecific symptoms such as fatigue and depression like symptoms. The typical symptoms are also less common in the elderly population. There is growing evidence that patients with OSA may be at increased cardiovascular risk. OSA may trigger or contribute to several cardiovascular disease, including hypertension, atrial fibrillation and congestive heart failure.

## Summary of Keypoints

- In this chapter, the clinical features and adverse consequences of OSA are reviewed. OSA is characterized by repetitive episodes of upper airway obstruction and is frequently found among adults.

- Risk factors : Obesity is the major risk factor for OSA through mechanisms such as fat deposition in the pharynx inducing airway narrowing and decreased tracheal tug. OSA prevalence increases up to the seventh decade. Men have a two to threefold higher prevalence of OSA than women in part due to central fat distribution, higher pharyngeal length and ventilatory instability.
- Symptoms: Loud, frequent, and irregular snoring are the most significant symptoms of OSA. Witnessed apneas is specific but is frequently not reported by the bed partner. Excessive daytime sleepiness, once thought to be the most important symptom of OSA, is only common among patients referred to sleep laboratories. In contrast, excessive daytime sleepiness is not common among patients with OSA and cardiovascular diseases as well as in community-based studies.
- Signs: Obesity is the most common sign of OSA and is more specific when centrally distributed as can be measured by neck and waist circumference determinations. A crowded pharynx as classified by the Mallampati scores III and IV is frequently observed in patients with OSA.
- Consequences of untreated OSA include excessive daytime sleepiness, fatigue, cognitive dysfunction, and impaired quality of life. OSA is frequently associated with cardiovascular and metabolic disorders. This association is explained not only by overlap of risk factors, such as obesity and male sex, but by the fact that OSA contributes to the development and aggravation of the underlying cardiovascular and metabolic diseases. Hypertension is the most studied cardiovascular consequence of OSA. OSA is now a recognized cause of secondary hypertension. In addition, OSA may contribute to arrhythmias, heart failure, insulin resistance, diabetes, dyslipidemia, and atherosclerosis progression. Untreated severe OSA is associated with increased risk of cardiovascular morbidity and mortality due to coronary artery disease and stroke.

## Chapter 7

# Assessments of Driving Risk in Sleep Apnea

Kingman P. Strohl

**Keywords** Driving risk • Automobile crashes • Sleepiness • Fatigue • Impairment

### Scope of the Problem

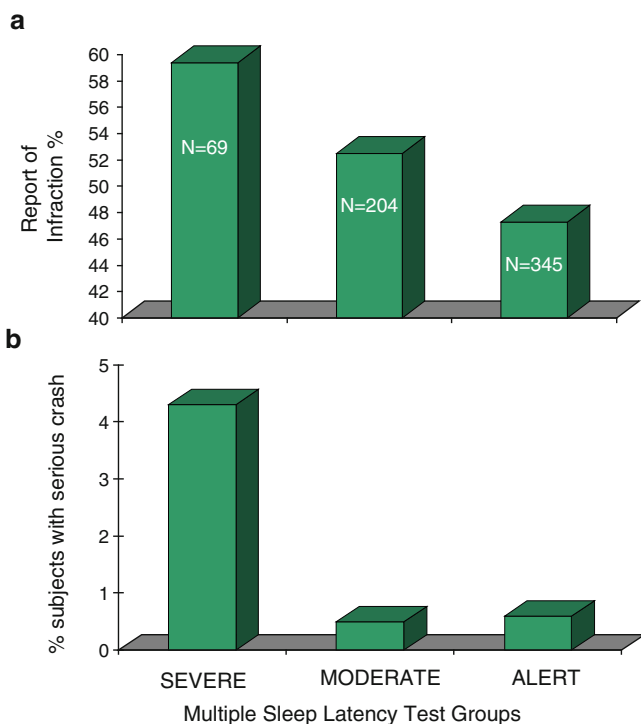
Sleepiness, also termed drowsiness, is defined by a set of neurocognitive behaviors within the state of wakefulness. It is rapidly reversible as is sleep, in contrast to states of stupor, coma, and anesthesia. Sleepiness in the wakefulness state can be defined by an attenuation of general vigilance associated with slowing of reaction times, not otherwise explained by neurologic or medical disease or exposure to medication, alcohol, and illicit drugs. Excessive waketime sleepiness is a risk factor to falling asleep abruptly, potentially with catastrophic consequences. One of the direct, functional outcomes of excessive sleepiness is that of impairment in driving performance and an increase in risk for drowsy driving and motor vehicle crashes, including traffic fatalities.

Fall-asleep accidents are generally inferred by the following characteristics. First, there is usually a pattern of drifting outside a lane to the right or left; second, there are no skid marks or apparent attempt to avoid a crash; and third, there should be no evidence for substance abuse [1]. Drug- or alcohol-related accidents can be determined from biologic samples, while sleepiness cannot. Often, there is a single driver. From compilation of records across several states and primary articles, sleep-related accidents, defined as above, are highest in males between the ages of 16 and 26 years, presumably because of risk-taking and other behavioral factors, followed by shift workers because of irregular and reduced sleep, and then by undiagnosed sleep disorders, like sleep apnea and narcolepsy [2, 3].

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**Fig. 7.1** Impact of sleepiness in a community sample. Shown here are data from Drake et al. [4] in two formats. The bars represent the groups according to MSLT category (see text) into severe (MSLT: 0.0 to  $\leq 5$  min), moderate (5–10 min), and alert ( $>10$  min). In (a) (top), there is shown the percent of subjects in each group where state driving records showed some traffic infraction or crash. The numbers on each bar represent the number of individuals. There appears a dose-response relationship ( $p=0.48$ ). In (b) (bottom), there is shown the number with severe injury accidents, those which prevent normal activities and require hospitalization. The severe group is significantly higher ( $p=0.05$ ) than the other groups

Excessive sleepiness is present in the general population. In a population-based healthy adult sample of Southeastern Michigan drivers [4], recruited subjects were divided into groups based on average multiple sleep latency testing (MSLT) latency as follows: severe (0.0 to  $\leq 5$  min; 11% of the sample), moderate (5–10 min; 33%); and alert ( $>10$  min; 56%). Prior 10-year state-documented rates for state motor vehicle reports were significantly different among groups (Fig. 7.1a). When the victim was the only occupant of the car, subjects with highest sleepiness had the greatest crash rate compared with alert individuals ( $p=0.022$ ). In the reporting of a severe injury, a higher prevalence ( $p=0.03$ ) was found in those who were excessively sleepy (4.3%) than in those who were moderately sleepy (0.5%) or alert (0.6%) (Fig. 7.1b). Thus, objectively “excessively” sleepy but healthy people appear to have had more crashes, and more severe crashes, in their driving history.

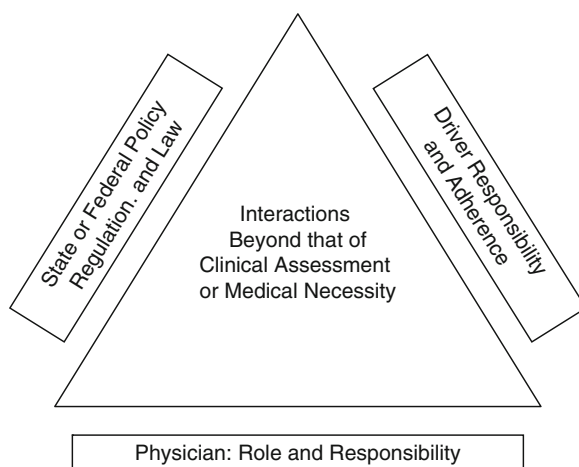
In those presenting for medical assessment, self-reported sleepiness is widespread. In a cross-sectional primary care survey of more than 6,000 waiting room patients, 24% reported sleepiness and 14% reported drowsy driving. There were regional differences (Europe vs. United States, and among various practices in the United States), and men (18.3%) reported drowsy driving more than women (9.8%). In this group, 34% met a risk profile for sleep apnea [5]. In a study in a Cleveland VA population using a similar methodology, 26% reported sleepiness and this correlated with Epworth Sleepiness Scale (ESS). While the mean ESS score (normal <11) was 8, over 40% had a score >11 and 4.6% had a score >17. Of these respondents, 47% met high-risk criteria for sleep apnea, 41% for insomnia, 19% for restless leg syndrome, and 4.7% for narcolepsy [6]. In another VA population using a similar methodology in Puerto Rico, 34% met high-risk criteria for sleep apnea, 53% for insomnia, 13% for symptoms suggestive of narcolepsy, and 13% for those suggestive of restless leg syndrome [3]. While it is unlikely that all of those with self-reports of symptoms will have disease, such individuals could be referred to pulmonary physicians or others with sleep expertise to be evaluated not only for a suspected disorder but also for management of excessive sleepiness.

There are some 40 articles on the subject “sleep apnea” as a categorical element for drowsy driving crashes. Two meta-analyses [7, 8] found that the majority of articles reported statistically significant, two- to three-fold risk between a diagnosis of sleep apnea and prior crash. For commercial drivers, only one of three studies found an increased crash rate, and this association was weaker (OR 1.3). The evidence was inconclusive regarding whether the risk was proportional to severity of the sleep apnea or to subjective daytime sleepiness. Treatment of sleep apnea appeared to reduce risk in a similar analysis of the exiting literature [9]. However, not all patients with sleep apnea have excessive daytime sleepiness [10] nor have experienced an automobile crash [11].

This article reviews publications from the past and present body of knowledge regarding pulmonary physician assessment and responsibilities for dominant symptoms of sleepiness and drowsiness. The diagnostic reasoning, clinical testing, and patient management issues for sleep disorders are described in greater detail in other chapters of this book. At issue here are the assessment and mitigation of drowsy driving and related accidents, injuries, and possible death. This is not a “how to” report but an annotated description of the landscape of decision-making and interactions that the pulmonary physician will have in this context of driving risk assessments (Fig. 7.2).

## Factors in Driving Risk

Driving a motor vehicle is a complex task that engages several physical and psychological skills; it is estimated that over a minute the driver in an urban setting makes 20–40 cognitive decisions a minute [12]. Driving certainly involves skills beyond that affected by sleepiness, including neurocognitive deficits associated with the



**Fig. 7.2** Interactions and parties to an assessment of driving risk. This graph depicts the relationships inherent in an assessment of driving risk and shows that the actions of the physician are performed in a broad context of interactions with society, in particular state and federal rules and regulations for driving privileges, and with the patient or client as an individual or as a member of society

co-morbidities of sleep apnea, such as hypertension, stroke, aging, medications for other chronic diseases, etc. [2, 12, 13]. Indeed a recent large study of medical outpatients concluded that in the absence of sleep apnea or other known sleep disorders, shift work and narcolepsy, independent predictors of excessive waketime sleepiness were ulcers  $OR=2.21$  (95%  $CI=1.35-3.61$ ) followed by migraines  $OR=1.36$  (95%  $CI=1.08-1.72$ ), and depression  $OR=1.46$  (95%  $CI=1.16-1.83$ ) after controlling for other conditions, age, gender, time in bed, caffeine, smoking, and alcohol use [14].

Obstructive sleep apnea (OSA) is associated with more crashes [8] and treatment with CPAP reduces crashes in patients with OSA by ~70% [9]. This finding is considered plausible given that driving simulator testing and reaction times consistently improve in those who are issued CPAP, especially in those who use it regularly (>4 h a night for >50–70% of nights). However, treatment may also result in greater alertness and vigilance while driving, despite little change in sleepiness [15] or less sleepiness but unchanged residual cognitive problems relating to planning and judgment [16]. One study used a driving simulator to determine how rapidly a person could respond to therapy and reported improvements in 2 days, but more benefit may accrue over several weeks [17]; however, it should be noted that poor performance on a simulator does not regularly predict a motor vehicle crash or accident [18].

An appropriate question is whether treatment of sleep apnea reduces risk to that of the general population [11]. Findley et al. was the first study to confirm with traffic records that patients being treated with nasal CPAP for sleep apnea had fewer automobile crashes and that the 2-year crash risk, while initially several fold higher, became that of the general population of the state of Colorado [19]. This study involved

50 patients with sleep apnea symptoms and AHI >15. While selection bias and regional specificity of the study limited broad conclusions, subsequent studies have confirmed this assessment [20]. Risk is reduced by recognition and treatment, perhaps even by an intent-to-treat [9].

## **The Interactive Responsibilities of a Driving Assessment**

Pulmonary physicians are expected to diagnose, treat, and assess illness, in general, and, with discovery of excessive or problematic waketime sleepiness, to recognize the potential impact of this symptom has on health and behavior. A particular element that would obligate the physician to intervene would be the presence of severe waketime sleepiness and a history of a previous motor vehicle accident or “near-miss” events that suspicion suggests is due to excessive sleepiness. This information alone is sufficient to immediately warn the patient of the potential risk of driving until effective therapy is instituted, and provide additional counseling to the family members. Not all patients suspected of having sleep apnea will present with a high level of sleepiness risk. Steps to reduce risk can be instituted awaiting diagnosis and treatment and a plan to assess the patient’s response with a goal of reducing risk to that of the general population.

When the physician informs the patient of the diagnosis and makes cautionary recommendations, the legal status of the patient as a motor vehicle operator is irrevocably changed. In the event that the patient thereafter has a traffic accident, the patient no longer can avoid civil and criminal liability by claiming that his falling asleep was sudden or unexpected [21]. For this reason alone, the physician should document his warning in writing, noting the reason for concern, or any recommendations specific to the individual patient [1]. Such an approach will reinforce the seriousness of the warning [2].

The pulmonary physician also is in a position to help the patient to restore his/her driving privileges whenever there is reasonable indication that the causes for excessive waketime sleepiness have been addressed including effective treatment. A restriction based on sleep apnea should not be regarded as permanent, in contrast to a diagnosis of narcolepsy.

Reporting responsibilities of the physicians will differ from one state to another, and according to the circumstances of a referral. Whether a report on a particular patient should be filed will depend on the state laws, policy, and regulations. Many state laws appear to allow room for a physician to report a patient if the physician believes the patient presents a current risk; but other state laws may obligate the physician to report based on diagnosis or symptoms alone. The physician is obligated to adhere to the requirements of the law in the specific state in which he or she practices, even if those laws do not reflect sound public policy or medical evidence.

In those instances in which the licensing agency has been notified about a patient’s condition (by the patient, physician, or anyone else), it is appropriate for the agency to consult a specialist with respect to the patient’s ability to operate a

motor vehicle. However, in the opinion of an expert panel convened by the American Thoracic Society, the physician is in no position to certify the patient's ability (fitness) to operate any motorized vehicle given the absence of training in motor vehicle licensure [1]. It is the DMV that has the legislated mandate to do this. However, the physician can comment on the nature and facts of the diagnosis, the facts concerning treatment, and the extent of treatment effectiveness.

There are inherent problems in the event that a sleep study or measures of sleepiness or performance are administratively requested to assess driving fitness. The first is that test outcomes are not closely linked to foreseeable driving risk. Even those assessments with MSLT in population noted in the Introduction were associated with retrospective crashes, and the differences between the highest and the lowest degrees of sleepiness may not necessarily drive policies in a democratic society or across states. The second is that there are rather loose correlation among AHI numbers, treatment effects, and drowsy driving because sleepiness is multifactorial, affected by sleep length, shift work, and medications even if the immediate medical condition, i.e., sleep apnea, is successfully treated. In one study, more than two-thirds of patients with sleep apnea had no reported crashes during a 5-year period [22]. Weight loss, fitness, avoidance of allergen exposure that produces allergic rhinitis, discontinuation of alcohol or another sedating medication, and more sleep opportunity and sleep time length can reduce sleepiness even if apnea number is not reduced. A third factor is that foreseen risk is affected by diagnosis even in the absence of institution of direct therapy. The patient and/or family will often institute reductions in risk exposure if discussed with the family [1].

Any authority requesting documentation of a clinical encounter should include a release indicating patient consent. It should also be noted in the release of data from polysomnography reports or titration results or trends in ESS values that these "snapshots" have not been shown to have predictive value in the prevention of an accident in an individual patient. As treatment vs. no treatment seems to be a key component, one could consider measures of CPAP compliance; but if a patient is treated by another mode of therapy, such adherence data are not available.

## **Potential for Liability Risk for Pulmonary Physicians**

Here the issue is how driving risk assessments are seen in the context of physician work. It is important to recognize that pulmonary physicians would be considered as being trained to assess and manage sleep apnea, in contrast to a primary care practitioner, or other nonsleep specialists. The expertise extends to a skill set in symptom assessment, including those of excessive sleepiness and the potential for drowsy driving present in some patients with sleep apnea. Therefore, a pulmonary physician would be expected to assess the degree of sleepiness and know what to do to mitigate risk.

As noted above the section on Factors in Driving Risk, identification of excessive driving risk by a point-of-service clinical assessment for sleep apnea is difficult. AHI values alone are not generally useful. In George et al. [23] the rate of prior



accidents/year, was highest in those with the highest AHI,  $>40/h$ , but many had not had an accident. Similarly, Horstmann et al. [24] found an increased motor vehicle accident rate only in patients with more severe SAS (AHI  $>34$ ). These were studies performed without controls. In the only follow-up case-control study of those with crashes, Kingshott et al. [25] reported that OSA drivers in crashes demonstrated significantly more driver sleepiness, slower reaction times and a trend for greater objective sleepiness compared with well-matched controls; however, controls showed moderate levels of unrecognized mild (5–15 AHI) sleep apnea as well. The implication was that sleep apnea was common in both controls and crash drivers and that the difference was in some other neurocognitive domain. However, there are no clinical methods or guidelines for routine neurocognitive testing in a pulmonary practitioner's office, so any approach using such tests is currently impractical. Therefore, the assessment will need to be at the point-of-service.

In the course of an evaluation, the patient/client and the physician are expected to act responsibly. While the physician is often trained to treat historical reports with some skepticism, there is an expectation that a patient will report to the best of their ability the symptoms and signs of disease, heed advice, and comply with therapy. Hence, it is important to inform the patient of the manner and purpose of the assessment and discuss the conclusions based upon the evidence. This is important especially if the visit is a 1-time assessment. Once informed of being at high risk for drowsy driving by a physician, failure by the licensed driver to take seriously suggested measures to reduce driving risk can carry consequences beyond the obvious threat to personal health. Such a failure to act can include a voidance of insurance and/or civil and criminal liabilities [21, 26–28].

The manner in which one informs the patient that he/she is at high risk is not established either in terms of customary practice nor for in the course of an administrative referral. The 1994 document from the American Thoracic Society suggested a form to be signed by a patient that the presentation was consistent with excessive waketime sleepiness and a high risk for drowsy driving, that this was discussed, and that in the opinion of the physician it was reasonable to reduce driving until such a condition was treated or sleepiness was reduced [1]. This approach has not been widely adopted, and in practice is difficult to institute as it carries no impact if the document is not signed. It is however appropriate to note in the office documentation that the topic was discussed on that day and what if any specific steps were suggested to reduce the high risk for drowsy driving. In the short term, such interventions as noted above could include advice about longer sleep opportunity, improved sleep hygiene, etc. In the long term, there might be more diagnostic testing or treatment.

Finally, in the event of a referral from a regulatory agency or its representative, including a commercial medical examiner, the visit is not based on medical necessity. In such instances, the cost of a physician visit and any testing may be denied. In addition, medical malpractice may not cover this interaction as it does not reflect a clinical problem or solution. In this instance, there may be more incentive for the driver to downplay symptoms of sleepiness or even of disease, not only to be eligible to drive but also to reduce expenses of testing. Hence, the circumstance of the referral is important to document the medical as well as administrative issues with clarity and attention to the consequences to the patient/client.

## Societal Implications

Sleep apnea is considered by many to be a “red flag” for reduced fitness to drive, but it should be pointed out that many persons with sleep apnea would still be considered safe to continue driving. The subsets which appear to present an elevated risk are those with excessive waketime sleepiness, rather than those categorically identified by either a diagnosis or a threshold number of events.

It may be potentially appropriate for commercial driver assessments to use the number of sleep apnea events or even a composite risk of associated traits (obesity, snoring, gender, and/or age) as triggers for concern; however, even this “screening” as its own problems given the prevalence of an AHI >5 in the population and the intersection of common elements (sleepiness caused by sleep restriction, obesity, medications for disease that produce drowsiness, snoring, etc.). For instance, BMI was recently proposed by a panel of medical experts to use BMI as an objective and identifiable risk for sleep apnea in commercial driver assessments. There is one study utilizing portable monitoring which identified only a BMI threshold of >30 as a risk factor (twofold higher accident rate per mile) for commercial drivers [29]. Whether a threshold BMI value is a viable option for routine testing in the absence of evaluation for ancillary signs and symptoms remains to be determined. In Ohio, 33% of the population of 20 million over the age of 16 years (potential noncommercial drivers) have a BMI >30, and the proportion of those seeking commercial licenses (150,000/year in Ohio alone) who have a BMI >30 is even higher. Routine testing for BMI alone is impractical. Furthermore, obesity has a socioeconomic dimension so that any assessment for risk based on BMI would have disproportionate, and potentially burdensome, effects on minority populations [30]. Such approaches would lead to unnecessary testing and added cost, and probably be unpopular.

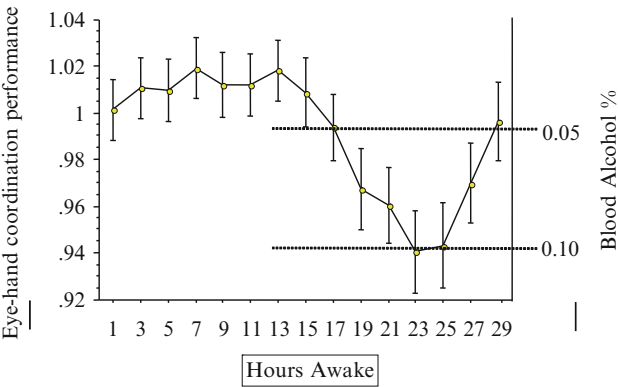
## Lessons from the Alcohol Literature

Up to this point, we have considered the case for assessment and management of excessive waketime sleepiness because of personal and societal risk. The data generally show that excessive sleepiness degrades driving skills and that some patients with sleep apnea will present with excessive waketime sleepiness. Finally, treatment of sleep apnea will reduce sleepiness and may reduce risk of drowsy driving to that of the general population. Thus, one concludes that excessive sleepiness is a substantial public health risk and steps need to be taken at regulatory and liability levels to reduce this risk. At this point, however, one should consider how a physician is asked to screen for another well-recognized risk factor for car crashes, namely alcohol.

Alcohol and sleepiness are similar in terms of effects that lead to “impairment,” the condition of being unable to perform as a consequence of physical or mental unfitness [27]. Both produce cognitive and eye–hand slowing of responses, limits decision skills, lead to increased errors of commission and omission, and declines

**Table 7.1** Comparison of effects on neurocognitive functions

Function	Alcohol	Sleepiness
Cognitive speed	Slowed	Slowed
Decision skills	Become limited	Become limited
Errors (commission and omission)	Increased	Increased
Eye–hand coordination	Slowing and errors	Slowing and errors
Divided task	Impaired	Impaired
Dose–response	Yes	Yes



**Fig. 7.3** Relative impairments of sleep deprivation and alcohol. This figure depicts the results in an eye–hand coordination task expressed as a percent of baseline over a 29-h period of sleep deprivation. Shown on the right vertical axis is the impairment at a given alcohol level in the same task. The data are adapted from Arendt et al. [32]

in divided-attention task (Table 7.1) [12, 31]. Both are accompanied by a lack of situational awareness of the degree of impairment, and both show dose-related effects, and there is an equivalency of impairment (Fig. 7.3) [32]. These adverse effects are reversed, the former by metabolism and the latter by adequate sleep or circadian rhythm. The effects of a combination of alcohol and sleepiness are more than additive [33]. Thus, in both conditions the physiology and pathophysiology are fairly well understood.

Driving while impaired by alcohol accounts for 32% of all traffic-related deaths [34]. Individuals with a first conviction for drunk driving have a high rate of recidivism, and about 30% of those involved in alcohol-related crashes have a prior arrest or conviction for the same offense [35]. Countermeasures at a public health level are directed at multiple levels – point-of-arrest sanctions, as well as assessments when treatment for a crash-related injury.

Laws regarding detection, reporting, and convictions for drunk driving exist in all states and territories of the United States [36]. There are efforts to improve technology

to detect alcohol levels while driving [37]. Moreover, there is a major push to publicize the risk and to educate the public on the dangers of drunk driving and the consequences of being discovered impaired by alcohol. The cost-effectiveness of these efforts are considered to be “modest” [38]. In this literature the emphasis is on detection and intervention at the first event, and prevention is aimed at general education, publicity, random testing, and stiff legal penalties. There is no general effort directed at physicians to predict and preempt drunk driving before it happens, but rather an effort to have physicians using historical evidence [35] or nurses in emergency room settings [39] intervene to reduce the next instance.

Legal remedies for drowsy driving are nonuniform across states. Prompted by an absence of a law to convict a driver after a death of a second party by his falling asleep at the wheel after >30 h of continuous wakefulness, New Jersey statute NJ H. R. 968, 2003 makes it an automatic felony charge if one has an accident after 24 h of sustained wakefulness [40]. Some 11 other states have had similar legislation drafted at a committee level and there has been an effort to make this a national regulation.

Using an analogy to alcohol risk to address excessive sleepiness, however, has several other problems. First, an objective, point-of-service measure for sleepiness in a driving crash is lacking. This makes it difficult to confirm or quantify for intervention. Second, the public is not prepared educationally about dangers of sleepiness in general and driving impairment caused by excessiveness sleepiness in particular. Admittedly there are efforts to publicize drowsy driving but these are directed at commercial sector, e.g., Parents against Tired Truckers and the Truck Safety Coalition, where the driving risk may actually be lower that for noncommercial drivers. Attention paid to the connections between extended hours of service and sleepiness in housestaff, but these are more often seen as special cases applicable to medical errors rather than drowsy driving and risk to the public. Third, the details of legal remedy will be difficult to implement across states. Alcohol limits and definitions of impairment are made at a state level. It took many years after the impairments of alcohol were well described to accomplish these legal standards state-by-state, and full implementation some 25 years ago was accomplished by tying acceptance of highway funds to the implementation of laws to regulate drunk driving [36]. Such a proposal to tie state efforts to reduce drowsy driving to availability of federal funds may not yet have sufficient political or social import compared to other issues. Thus, not only is it difficult to identify and quantify drowsy driving, but the groundwork for acceptance of drowsy driving as a public risk as impairment and at the same plane as drunk driving is lacking.

At the present time, an informed general public about the effects of sleepiness and the effectiveness of sleep as a countermeasure is of highest priority prevention of motor vehicle crashes, unintended injury, and/or unintended death from excessive waketime sleepiness. Such an effort is necessary to implement formal medical assessments or any punitive measures designed to reduce risk. Information on drowsy driving should be incorporated into educational and evaluation materials for licensing and operation of noncommercial vehicles.

## Principles in Assessment of Risk by the Pulmonary Physician

Under general principles of malpractice liability, physicians are obligated to adhere to the prevailing standard of care [2]. Pulmonary specialists are expected to be aware of the presentations and complications of excessive sleepiness, of which sleep apnea is a common cause.

At the present time, driving risk is considered elevated by the presence of moderate and severe sleepiness, as based upon historic information from the patient or an informed observer, of which the strongest evidence is a history of a previous motor vehicle crash, and response to therapy is also judged similarly [1]. There is no reliable objective test that is predictive of increased driving risk or that would indicate that, after treatment, driving risk has been reduced to an acceptable level. Asking direct questions of driving risk in the context of a clinical examination is subject to driver bias and physician interpretation of the history. Of course, retrospection by the patient or family after treatment may have identified higher potential risk before treatment. These general observations make it difficult to assign to an individual risk before treatment, and are more useful in supporting continued treatment and management of the primary cause, be it sleep apnea or sleep restriction or voluntary cessation of driving.

Triggers for direct questioning of the presence of active sleepiness might be either a high ( $>17/24$ ) ESS score, a personal report of excessive sleepiness interfering with activities of daily living, or family report of drowsy driving. In the opinion of the committee, a time span limited to “recent times” is appropriate, rather than lifetime exposure. Subjective rating scales, such as the ESS, can be used in clinical and epidemiological settings [11]. The eight questions of the ESS ask about the tendency to fall asleep in recent times, but these circumstances are passive in nature. They do not ask for instances of sleep attacks that occur while a person is trying to do something, i.e., active sleepiness. Also, their usefulness is limited; for instance, the ESS cannot be used to demonstrate or exclude sleepiness as it is measured by objectively [41]. Recently, a single simplified question was piloted against ESS and objective testing and found to have some internal validity [42]. This question “Please measure your sleepiness on a typical day” was rated from 0=none to 10=highest. Scores  $\leq 2$  or  $\geq 9$  reliably predict normal or abnormal ESS scores, respectively. Since the ESS is not commonly used in nonsleep specialized practices, this simplified screening question was proposed as a useful screening tool for patients with disorders of sleepiness.

The American Thoracic Society committee report identified that the common elements for assessment are: notation of initial severity in clinical terms; assessment of sleepiness by ESS and initially direct questions about drowsy driving; time estimate for or of diagnosis and time estimate for or of initiation of therapy; type of therapy including behavioral interventions, as appropriate; specific notation of the start of therapy by Positive Airway Pressure or other instituted therapy; documentation of adherence to Positive Airway Pressure Therapy or, as appropriate, the response

to another therapy, as appropriate; and reassessment of drowsy driving, if the patient was at any prior point in time at high risk.

A point of service assessment often cannot be dependent on outside information to be obtained later. While it is advocated that family members or others provide additional insight about sleep and sleepiness at the time of the initial evaluation, it is not required that the physician wait to make an assessment if such information is not available at the time of risk assessment. Setting aside issues of patient release and of physician knowledge of how to interpret such results, obtaining an official driving record might not arrive in a timely manner, given the need for proper release of information and bureaucratic inertia. Waiting for PSG results is not an attractive alternative as knowing the AHI and then assigning risk puts the patient into double jeopardy; if the patient was not deemed a risk before a diagnostic sleep study, then how could he/she be one after the study. Likewise, the assessment of risk after initiation of therapy should be performed in those deemed at highest risk before initiation of therapy. Treatment, even intent-to-treat, may reduce risk.

## Summary of Keypoints

- Sleepiness, also termed drowsiness, is defined by a set of neurocognitive behaviors within the state of wakefulness.
- A direct, functional outcome of excessive sleepiness is impaired driving performance and increased risk for drowsy driving and motor vehicle crashes, including fatalities.
- In regard to sleep apnea, whether crash risk is proportional to apnea severity or to subjective daytime sleepiness is at present unknown, as there are multiple other causes for sleepiness and inattention.
- While in small studies treatment of sleep apnea appeared to reduce risk, not all patients with sleep apnea have excessive daytime sleepiness nor have experienced an automobile crash.
- Physician assessments at the point of service would have a purpose to mitigate drowsy driving; however, the advice here is anecdotal.
- This chapter is an annotated report of the landscape of decision-making that the pulmonary physician will encounter in the context of driving risk assessments.

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## Chapter 8

# Nasal Continuous Positive Airway Pressure (CPAP) Treatment

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**Keywords** Continuous positive airway pressure • CVPAP titration • Adherence • Cognitive behavior therapy • Daytime hypersomnia • Motor vehicle accidents

### Mechanisms

Continuous positive airway pressure (CPAP) remains the treatment of choice for patients with obstructive sleep apnea (OSA). The mechanism by which CPAP maintains the patency of the upper airway in patients with OSA is by acting as a pneumatic splint. The authors of the paper introducing CPAP as a treatment modality for OSA suggested this mechanism in 1981 [1]. Subsequent research explored other mechanisms and confirmed this notion and showed that CPAP can increase upper airway volume by ~20% [2]. CPAP does not stimulate upper airway dilator muscle activity as shown by electromyography (EMG) of alae nose or genioglossus [3]. In another study seeking to understand the airway changes induced by CPAP, the authors reported increase in increased lateral airway dimensions rather than antero-posterior dimensions due to a reduction in pharyngeal wall thickness. Soft palate and tongue did not show significant changes [4]. Finally, CPAP also increases lung volume, although this effect alone is not adequate to treat OSA due to the upper airway obstruction [5].

The optimal pressure required to eliminate OSA is inversely related to increasing age and increasing lung volumes [6]. Room air is pressurized in the device and delivered through an interface to the patient's airway. Intermittent collapse of the

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pharyngeal airway is a key component in the pathophysiology of OSA. The patency of the pharyngeal airway depends upon the balance between the intraluminal and extraluminal forces that act in opposite directions. We can understand this concept by the Starling resistor model. Based on this model, critical pharyngeal pressure ( $P_{crit}$ ) is negative in normal individuals during sleep, while it is positive in patients with pharyngeal airway collapse [7–9].  $P_{crit}$  is influenced by physical factors like peripharyngeal pressure [10] as well as lung volumes, and varies inversely with end-expiratory lung volume [11]. This model provides a conceptual platform for the basis of CPAP treatment. The objective of a CPAP titration study is to gradually increase the pressure applied at the nose until there is resolution of pharyngeal airway collapse. This occurs when the pressure applied at the nose exceeds the  $P_{crit}$ .

## Beneficial Effects

CPAP has shown to be beneficial based on several outcome measures in patients with OSA. Examples of these are outlined below.

### *Excessive Daytime Sleepiness*

Excessive daytime sleepiness (EDS) is a major symptom of patients with OSA. Improvement in EDS would be a visible testimonial of the effectiveness of CPAP in the treatment of OSA from the patient's perspective. Several studies have addressed the beneficial effect of CPAP on EDS in patients with OSA. Yamamoto et al. studied 47 patients with OSA and concluded that CPAP improves EDS in patients with OSA [12]. A Cochrane review of 36 trials involving 1,718 people concluded that compared with control, CPAP therapy demonstrated significant improvements in both objective and subjective sleepiness measures [13]. Interestingly a study of 55 patients with severe OSA [apnea hypopnea index (AHI) of greater than 30 events/h] and no daytime sleepiness showed that CPAP was not effective in improving objective measures of sleepiness, cognitive function, or blood pressure [14]. This finding highlights the importance of viewing the diagnosis of OSA, as not limited to a number, i.e., AHI, especially when there is no associated daytime sleepiness. AHI can vary from night to night, it is inversely related to the length of each individual apnea or hypopnea, and hence a lower AHI or high AHI gains significance only when associated with clinical consequences which includes EDS.

### *Blood Pressure*

Systemic hypertension is perhaps the most studied and well-documented consequence of OSA. Several mechanisms, including excessive sympathetic discharge, vascular

inflammation, oxidative stress and endothelial dysfunction may be contributing to the development of systemic hypertension in patients with OSA. It then makes mechanistic sense that CPAP treatment of OSA may improve blood pressure control by reversing these abnormalities. Several studies evaluated the effectiveness of CPAP treatment in BP control over the last 2 decades. A meta-analysis of 12 randomized control trials which included 572 patients showed that CPAP treatment was effective in reducing the mean 24-h ambulatory blood pressure [15]. Similarly, Jaimcharitam et al. demonstrated that CPAP treatment improves blood pressure even in mild OSA patients [16].

### ***Pulmonary Hypertension***

OSA is considered in class III of World Health Organization (WHO) classification for pulmonary hypertension (PH) [17]. The mechanism by which OSA likely causes increases in pulmonary artery pressures is through hypoxemia. It then follows that treatment of OSA using CPAP may improve the PH by eliminating the associated hypoxemia. In a randomized crossover trial of 23 middle-aged patients with OSA, echocardiographic measurements of pulmonary artery systolic pressure and urinary catecholamine levels were higher in OSA patients than in controls, and improved with CPAP treatment [18]. These findings are in agreement with earlier studies that showed improvement in pulmonary arterial pressure as well as hypoxic pulmonary vascular reactivity after CPAP treatment in patients who had OSA but were otherwise healthy [19].

### ***Heart Failure***

The benefits of CPAP in patients with heart failure may extend beyond the effect of increased lung volume. In a prospective study, 24 patients with OSA and coexisting congestive heart failure were randomly assigned CPAP or medical treatment alone [20]. The CPAP group showed improved blood pressure, heart rate associated with improved OSA. The left ventricular ejection fraction improved from  $25.0 \pm 2.8$  to  $33.8 \pm 2.4\%$  ( $P < 0.001$ ). In another multicenter study, 60 patients with chronic heart failure showed improved cardiac output in 3 months after CPAP treatment. The improvement was significant in patients with LVEF greater than 30% [21].

### ***Cardiac Arrhythmias***

Cardiac arrhythmias, including atrial fibrillation (AF), have been reported in patients with OSA. In a landmark study by Kanagala et al., patients with AF and OSA who

were about to undergo treatment with cardioversion were studied prospectively for recurrence of AF after treatment of OSA [22]. Rates of recurrence of AF were compared among three groups: treated OSA, untreated OSA, and a control group. Recurrence of AF at 12 months in the untreated OSA group ( $n=27$ ) was 82%; in the treated OSA group was 42% ( $n=12$ ,  $P=0.013$ ); and in the control patients 53% ( $n=79$ ,  $P=0.009$ ). The nocturnal fall in oxygen saturation was greater ( $P=0.034$ ) in those who had recurrence of AF ( $n=20$ ) than in those without recurrence ( $n=5$ ). CPAP treatment may reduce or resolve the arrhythmias by resolving the obstruction and related consequences. However, large randomized studies are lacking in this regard.

### ***Neurocognitive Function***

In a randomized control trial, 46 patients with OSA were randomized to receive supplemental oxygen, sham CPAP, or therapeutic CPAP [23]. A battery of tests of neurocognitive function was performed. A 2-week trial of therapeutic CPAP improved speed of information processing, vigilance, and sustained attention and alertness. In a separate study, a subset of patients with Alzheimer's disease was shown to experience improvement in neurocognitive function and memory [24]. However, all the outcomes are not necessarily positive. In a prospective study, 37 patients with severe OSA were compared with normal controls in terms of neuropsychological measures of complex attention, executive function, and psychomotor speed. The OSA group fared worse when compared to the control group even after CPAP treatment suggesting that some cognitive deficits may be resistant to treatment [25]. At this time, a multi-center prospective study sponsored by the National Heart Lung and Blood Institute (NHLBI) called Apnea Positive Pressure Longterm Efficacy Study (A.P.P.L.E.S.) is underway. This study focuses on the effectiveness of CPAP on memory, learning, sleepiness, mood, and quality of life. It is hoped that the results of this study will shed further light on the effect of CPAP on neurocognitive function.

### ***Glucose Metabolism***

OSA may affect glucose metabolism via the pathway of intermittent hypoxia. Insulin sensitivity is the amount of insulin required to maintain normoglycemia when a subject is given a glucose challenge. Impaired insulin sensitivity or insulin resistance suggests predisposition to diabetes or may be part of the metabolic syndrome. At least four studies of almost 900 type 2 diabetic patients suggest a prevalence of OSA in that population of 73% [26–29]. Such observations raised interest in the potential relationship between OSA and diabetes, and consequently the possibility of improvement or resolution of diabetes with treatment of coexisting OSA. Studies to date examining the effects of CPAP on glucose control show

conflicting results. Babu et al. investigated obese, diabetic patients ( $n=25$ ) and showed that after 3 months of CPAP there was improvement in HbA1c and post-prandial glucose levels which were better in those using CPAP more regularly [30]. Improvements in nighttime glucose levels during one night and 5 weeks of CPAP use have been shown in two other studies [31, 32]. Three other studies, however, did not show significant changes in HbA1c levels, but two of them did document some improvement in insulin sensitivity [33–35].

### ***Motor Vehicle Accidents***

OSA is associated with increased risk for motor vehicle accidents. Excessive sleepiness and impaired reflexes due to sleep deprivation may play a role in the increased risk. In a study of 80 patients with OSA and 80 control subjects, patients with OSAS had a 2.6-times higher risk of suffering a motor vehicle accident than controls (rate ratio,  $RR=2.57$ ; 95% confidence interval,  $CI=1.30–5.05$ ) [36]. The rate of accidents was reduced more than 50% in patients with OSA ( $RR=0.41$ ; 95%  $CI=0.21–0.79$ ), although this also occurred in controls in this study ( $RR=0.49$ ; 95%  $CI=0.17–1.40$ ). Another study has showed that the increased risk for motor vehicle accidents was reduced after 3 months of CPAP treatment [37].

### **Adverse Effects**

Patients using CPAP will complain of nasal dryness, rhinorrhea, and less commonly, epistaxis. Flow-related side effects may include chest discomfort, aerophagia and feeling of “smothering” due to difficulty exhaling against the pressure. The mask may cause skin allergies or facial abrasions. Conjunctivitis due to the airflow can occur. These adverse affects can range from minor inconvenience to significant interference with therapy and result in nonadherence. Regular clinical follow-up with careful attention to the adverse effects is important in ongoing treatment of OSA utilizing CPAP.

### **Setting Up CPAP**

When initiating CPAP, there are numerous options available. The current standard is to perform a single overnight polysomnogram while the patient is monitored so the attendant can increase CPAP levels to progressively eliminate disordered breathing events. However, split night studies, autotitrating PAP devices, and other empiric methods of initiating CPAP are also available.

## ***Titration***

The current gold standard is a full-night-monitored CPAP titration in a sleep laboratory. Patients are set up to undergo polysomnogram. The CPAP is generally initiated at a setting of 5 cm of water after appropriate measurement of the facial area and mask fit. The CPAP setting is gradually titrated in increments of 1–2 cm of water at a time. The titration is guided by resolution of snoring, resolution or substantial improvement in airflow pattern and apneas and hyponeas as well as tolerance by the patient. Central apneas are sometimes seen with CPAP titration. These are usually self-limited. An ideal titration should include adequate time at each setting and also include supine and REM sleep. OSA tends to be more severe in the supine position and during REM sleep and achieving a pressure setting that is adequate in the supine and during REM sleep is an important consideration. Some studies are “split,” i.e., in a patient with severe OSA that meets the preset criteria for severity, the definition of which will vary among sleep laboratories, the CPAP titration is initiated after at least 2 h of a diagnostic study.

## **Auto Titration**

With increasing demand for services and difficulties associated with access to sleep laboratories and costs, there has been interest in performing out of sleep center titrations utilizing autotitrating PAP machines. In selected patient groups without serious comorbidities, these devices may be adequate. Autotitrating PAP (APAP) has been advocated as an alternative to traditional CPAP titration. The laboratory-based titration may be limited by night-to-night variability in pressure requirement, the inconvenience of laboratory environment, costly nature of sleep studies, and the time lag between diagnosis of OSA and institution of therapy. A meta-analysis of nine randomized controlled trials involving 292 patients showed that while APAP reduced the mean pressure by 2.2 cmH<sub>2</sub>O, it was equivalent but not superior to traditional titration in terms of adherence, ability to eliminate respiratory events and EDS as measured by Epworth sleepiness scale scores [38]. Two groups of patients in whom autotitrating PAP may not be appropriate include patients with serious cardiopulmonary illness and patients with obesity hypoventilation syndrome. The APAP machines algorithm will increase the pressure settings within a preset range based on flow limitation. The above-mentioned patients may have persistent hypoxemia which may not be detected by the APAP machines. Additionally, mouth breathing or leaks may be recognized as flow limitation resulting in inappropriate increase in pressure which may exacerbate the leak resulting in a vicious cycle. The current recommendations by the American Academy of Sleep Medicine Taskforce practice parameters are reproduced in Table 8.1 [39]. At this time, APAP cannot be recommended as first-line therapy in all patients with OSA.

**Table 8.1** AASM recommendations for APAP use [39]

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APAP devices are not recommended to diagnose OSA
Patients with congestive heart failure, patients with significant lung disease such as chronic obstructive pulmonary disease; patients expected to have nocturnal arterial oxyhemoglobin desaturation due to conditions other than OSA (e.g., obesity hypoventilation syndrome); patients who do not snore (either naturally or as a result of palate surgery); and patients who have central sleep apnea syndromes are not currently candidates for APAP titration or treatment
APAP devices are not currently recommended for split-night titration
Certain APAP devices may be used during attended titration with polysomnography to identify single pressure for use with standard CPAP for treatment of moderate to severe OSA
Certain APAP devices may be initiated and used in the self-adjusting mode for unattended treatment of patients with moderate to severe OSA without significant comorbidities (CHF, COPD, central sleep apnea syndromes, or hypoventilation syndromes)
Certain APAP devices may be used in an unattended way to determine a fixed CPAP treatment pressure for patients with moderate to severe OSA without significant comorbidities (CHF, COPD, central sleep apnea syndromes, or hypoventilation syndromes)
Patients being treated with fixed CPAP on the basis of APAP titration or being treated with APAP must have close clinical follow-up to determine treatment effectiveness and safety
A reevaluation and, if necessary, a standard attended CPAP titration should be performed if symptoms do not resolve or the APAP treatment otherwise appears to lack efficacy

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**Predictive Equations and Bedpartner Titration**

A major prerequisite to the evaluation of different alternative modes of CPAP titration is a clear picture of what constitutes optimal titration. While we target several parameters, e.g., elimination of snoring, resolution of defined apneas and hyponeas or normalization of flow patterns, there is no unambiguously defined gold standard criterion that can be a universal target. Using predictive equations and bedpartner-assisted self-titration of CPAP at home are intriguing ideas. In a prospective study of 1,111 patients Schiza et al. showed that the predicted CPAP pressure calculated using the Hoffstein formula, which utilizes body mass index, neck circumference and AHI, was close  $\pm 2$  cm of water to the pressure obtained by CPAP titration in 79% of the subjects [40]. The authors also tested their own formula which included the additional variables of smoking history and gender and report a successful prediction that correlated with the final CPAP pressure in 95% of the subjects.

**CPAP Modifications**

CPAP tolerance and acceptance can be improved by additional modifications that include “ramp” function in which the initial pressure is lower than the desired pressure and gradually increases to the desired pressure over a set time frame, presumably while the patient is falling asleep. Adding humidity to the inspired air can help avoid

nasal dryness. Pressure relief positive airway pressure (PRPAP) is an advanced technological option to CPAP therapy. Respirationics developed the first C-Flex device (C-Flex™; Respirationics, Murrysville, PA, USA). It has three levels of comfort. The maximum pressure drop is level 3 which is about 3 cmH<sub>2</sub>O. ResMed (Sydney, Australia) have developed a similar technology called expiratory pressure relief (EPR). One study showed that C-Flex™ may improve treatment adherence [41], while according to another study it was only comparable to traditional CPAP in terms of efficacy and, at a higher cost [42].

Bilevel PAP involves setting different inspiratory (IPAP) and expiratory pressures (EPAP). A bilevel setting may be appropriate in patients who have persistent hypoxemia due to obesity hypoventilation syndrome or intrinsic pulmonary disorders. Bilevel PAP is typically initiated by using the CPAP level that eliminated the obstructive apneas as the EPAP and EPAP + 3–5 cm of water as the IPAP. A retrospective analysis of several studies with a combined number of 719 subjects showed that bilevel PAP may worsen central apneas in patients with OSA and thus may be less desirable than CPAP for its treatment [43].

## Adherence

Adherence to therapy is a key ingredient of any therapeutic relationship between health care providers and patients. Patient adherence is modest at best, with any therapeutic intervention including oral medications for chronic diseases like hypertension. Adherence with CPAP is comparable to other chronic diseases. Older age and 1 time use of a sedative hypnotic were statistically significant predictors of compliance with CPAP usage ( $P < 0.005$ ) [44]. A review of the ethics of compliance introduces provocative perspectives into the issue of compliance and adherence and suggests that the debate so far has not taken patient's perspective into consideration [45]. A broad-based approach that involves the patient as an important component in the therapeutic decision-making process should be encouraged. A randomized control trial of 100 patients showed that cognitive behavior therapy (CBT) improved initial use as well as adherence to CPAP therapy [46].

## Conclusion

CPAP is the first-line therapy for OSA. CPAP keeps the airway open by acting as a pneumatic splint. CPAP treatment of OSA results in several health benefits. The appropriate pressure that can resolve the upper airway obstruction is classically derived by a CPAP titration polysomnogram. Predictive equations exist which may closely approximate the final setting derived by CPAP titration. Autotitrating CPAP, bilevel PAP, and flexible PAP are some of the modified PAP options.



## Summary of Keypoints

- CPAP is the first-line therapy for OSA. CPAP preserves upper airway patency by acting as a pneumatic splint.
- The appropriate pressure that can resolve the upper airway obstruction is classically derived by a CPAP titration polysomnogram. Predictive equations do not obviate the need for a titration study.
- CPAP remains the treatment of choice for patients with OSA.
- CPAP treatment leads to amelioration of several adverse consequences of sleep apnea including amelioration of daytime sleepiness and decreased rate of motor vehicle accidents. The effect on cognitive function is less clear.
- Hemodynamic and metabolic benefits of nasal PAP therapy include improved systemic blood pressure, improved systolic heart function, and decreased cardiac arrhythmias.
- Adverse effects of PAP therapy include nasal dryness, rhinorrhea, chest discomfort, facial abrasions, and conjunctivitis. The adverse effects are usually mild and easy to manage.
- Adherence with nasal CPAP therapy is suboptimal but comparable to other treatments for chronic disease. To optimize adherence, therapeutic decision-making process should include the patient at every step. CBT may improve initial use as well as adherence to CPAP therapy.

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## Chapter 9

# Obstructive Sleep Apnea: Oral Appliances

Peter A. Cistulli, Kate Sutherland, and Andrew S.L. Chan

**Keywords** Obstructive sleep apnea • Oral appliances • Mandibular advancement  
• Dental devices • Upper airway

### Introduction

Oral appliances are increasingly being used for the treatment of obstructive sleep apnea (OSA) and are a simpler alternative to continuous positive airway pressure (CPAP) [1]. Although CPAP is highly efficacious, the obtrusive nature of the mask interface results in suboptimal patient compliance, limiting its clinical effectiveness. This has stimulated interest in alternative treatment strategies which are more acceptable to patients and oral appliance therapy is one such approach. Oral appliances protrude and hold the mandible and/or tongue in a forward position. This anatomical adjustment reduces the propensity for upper airway collapse during sleep through alteration of airway structure and function. The advantages of this form of therapy compared to CPAP are simplicity, portability, lack of noise, or need for a power source and a potentially lower cost. Oral appliances were first described as a treatment for OSA some 20 years ago. However, the last decade has produced a substantial evidence base validating their therapeutic use [2]. Oral appliances are now recommended as a first-line therapy for OSA in selected patients and as patient preference generally favors this form of treatment compared to CPAP, their clinical use will likely continue to grow in coming years. This chapter will provide an overview of the field.

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## Types of Appliances

Oral appliances can be categorized by design into two main types; mandibular advancement splints (MAS) and tongue retaining devices (TRD). MAS attach to the upper and lower dental arches and mechanically protrude the mandible. TRD feature a preformed bulb into which the tongue is inserted and held by suction in a protruded position. Within each of these oral appliance categories there are numerous variations in design features and specifications.

MAS (also known as mandibular advancement devices or mandibular repositioning appliances) are by far the most commonly used oral appliance for OSA treatment in clinical practice today. Although all appliances of this type maintain the mandible in a protruded position, there are differences in how this is achieved between individual designs. Most broadly, MAS can be distinguished by their configuration as either a one-piece appliance (monobloc) or a two-piece appliance (duobloc) consisting of separate upper and lower plates. Apart from this design distinction, appliances differ in size, type of construction material, the amount of occlusal coverage, degree of customization to a patient's dentition, amount of vertical and lateral jaw movement permitted, allowance of oral breathing, and degree of titratability of advancement. The coupling mechanism between the plates of two-piece appliances can also differ in location and type, from elastic or plastic connectors, metal pin and tube connectors, hook connectors, acrylic extensions to magnets. Two-piece appliances have the advantage of greater adjustability and therefore allow a greater range of mandibular protrusion to be achieved more comfortably; however, one-piece splints are sometimes indicated due to dental conditions or the occlusal relationship.

Currently little is known about the influence of these design differences on clinical outcomes, although such variations are likely to influence efficacy, adverse effects, and patient compliance and are therefore important in device selection. Compared to prefabricated "boil and bite" type models, custom-made and adjusted appliances are associated with better retention in the oral cavity, greater patient comfort, and efficacy in improvement of OSA [3].

TRD all feature a flexible bulb, which upon insertion of the tongue, can be squeezed to generate negative suction pressure by the displacement of air. The suction retains the tongue in a forward position, preventing its collapse back into the oropharyngeal airway. In original TRD designs, the anterior bulb is fixed to a covering of the upper and lower dental arches, similar to a mouth guard. These TRD can be custom-made from impressions of the upper and lower dental arches of individual patients or be preformed "boil and bite" type appliances which the patient can fit themselves. A more recent design eliminates the need for any dental coverage as the bulb is held forward by external vertical flanges placed outside the lips [4]. A role for TRD has been proposed as a treatment option for those patients who are precluded from MAS therapy due to dental issues (e.g., edentulous patients) as retention of this appliance is not dependent on the teeth. Furthermore, customized

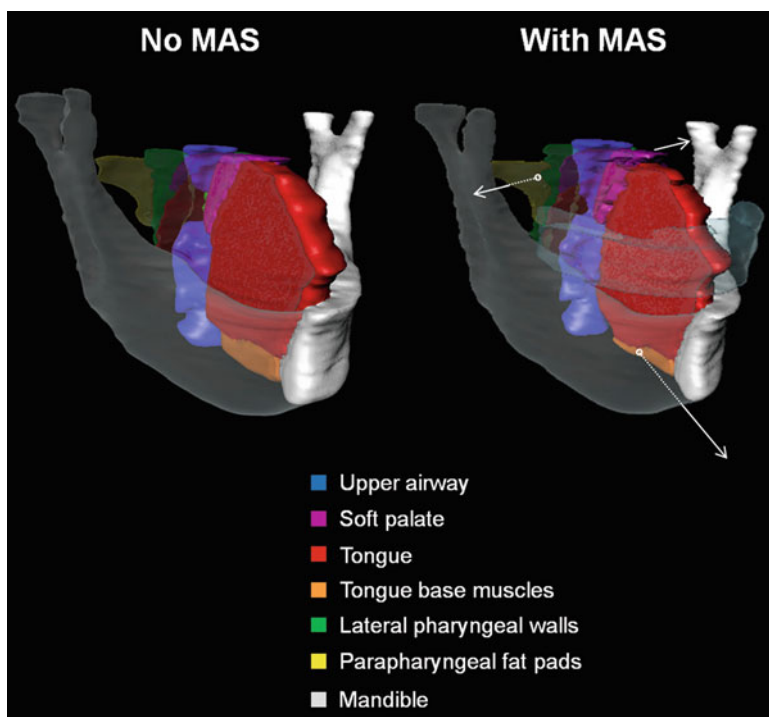
hybrid-type appliances have emerged, which combine an anterior tongue retention bulb with defined mandibular protrusion achieved through the upper and lower dental covering [5].

## Mechanism of Action

The objective of oral appliance treatment for OSA is to improve airway patency and prevent upper airway collapse during sleep. MAS have been shown to decrease upper airway collapsibility [6] and this improvement in upper airway function is dependent on the advancement of the mandible as control appliances which do not provide any protrusion are ineffective in reducing apnea-hypopnea index (AHI) [7, 8]. Although the mechanical advancement of the mandible reduces the propensity of the upper airway to collapse, by what mechanisms this is achieved is still not well understood. Intuitively the effect of MAS on the upper airway has been attributed to the forward movement of the mandible and/or tongue producing increased anteroposterior dimensions of the retrolingual airway. However, recent imaging studies, using techniques such as magnetic resonance imaging (MRI) and nasopharyngoscopy which allow visualization of the cross-section of the airway lumen have contradicted this theory [9, 10]. It appears that the greatest effect of MAS on upper airway structure is in the velopharynx, behind the soft palate. Furthermore, the largest increase in airway diameter occurs in the lateral, not anteroposterior, dimension [10]. Although initially counterintuitive, soft tissue connections exist between the mandible, tongue, and lateral pharyngeal walls and soft palate within the palatoglossal and palatopharyngeal arches. The stretching of these connections by mandibular advancement has been proposed as a potential mechanism by which MAS increases velopharyngeal patency and stability. Upper airway structural changes with MAS are illustrated in Fig. 9.1.

In addition to these anatomical effects it is possible that MAS may influence upper airway neuromuscular function. Research studies have demonstrated an increase in genioglossus muscle activity with MAS [11, 12]. Although the data is limited, stimulation of neuromuscular reflex pathways by MAS may further contribute to upper airway stability during sleep. The relative importance of anatomical vs. neuromuscular responses to MAS may also vary between individual patients.

The mechanisms of action of the more infrequently used TRD appliances have received even less attention although they likely differ from that of MAS. TRD increases upper airway dimensions to a greater extent than MAS due to the greater anterior movement of tissue produced by retaining the tongue outside the oral cavity [13]. The relevance of these greater structural effects with TSD to treatment efficacy warrants further study. In this MRI study, although TSD was shown to increase retrolingual dimensions, the greatest impact on airway structure was in the velopharynx. Velopharyngeal volume was increased by expansion of both the lateral and anteroposterior diameters, suggesting that in addition to forward displacement of the



**Fig. 9.1** Mechanisms of action of MAS. Upper airway volume is increased with MAS. This change in airway structure is associated with movement of surrounding soft tissue structures. Analysis of the movement of soft tissue centroids (a point analogous to the center of mass of a 3D structure) shows anterior displacement of the tongue base muscles and lateral movement of the parapharyngeal fat pads away from the airway with MAS wear

tongue, stretching of other soft tissue connections may contribute to enlarging other dimensions of the upper airway. Moreover, it is possible to TRD counteract the effect of gravity on the tongue in the supine position.

## Efficacy and Effectiveness in the Treatment of OSA

That MAS are able to significantly improve OSA across a range of severities has now been established by multiple randomized controlled trials. Several recent systematic reviews of the efficacy and effectiveness of MAS also exist [14–17].

### *Impact on Polysomnographic Outcomes*

Success rates in reducing AHI obviously vary with the definition of success used. The inclusion of a rigorous definition of treatment success seems most appropriate



given that resolution of OSA is the ultimate goal of treatment. By stringent definition of a complete response (reduction of AHI to less than 5/h), 35–40% of patients achieve treatment success. However, a further 25% display a partial response with a reduction in AHI of greater than 50% but with a residual AHI remaining above 5/h. Approximately 35–40% of patients will not respond to treatment (less than 50% AHI reduction) and some patients experience an elevation in AHI with MAS treatment [7, 8, 18, 19]. However, as these figures indicate, around two-thirds of patients will receive clinical benefit from MAS therapy.

Improvements in other polysomnographic indices have also been demonstrated with MAS. Measures of oxygen saturation generally show some improvement [20, 21], although the changes are less impressive than the effects on AHI, with oxygen saturation rarely increased to normal levels. Improvements in sleep architecture [7] and arousal indices [8, 20, 22] are also demonstrated.

### *Impact on Health Outcomes*

The effects of MAS on daytime sleepiness have mostly been assessed subjectively using the Epworth Sleepiness Scale. Although generally improvements in Epworth Sleepiness scores are observed [23–25] the magnitude is often small and some studies have identified a placebo effect on subjective sleepiness with use of an inactive oral appliance [7, 8]. Studies including objective measures of sleepiness are more limited, but MAS appears to have equivalent effects to CPAP with regard to performance in the maintenance of wakefulness test (MWT) [25, 26] and the Oxford sleep resistance (OSLER) test [23]. MAS have also been shown to improve simulated driving performance to a similar extent to CPAP [27].

The effects of MAS on neurocognitive functioning have only been assessed in a small number of studies and warrant further investigation. Compared to an inactive oral appliance, MAS treatment improved performance in tests of vigilance/psychomotor speed but did not change other neurocognitive measures [28]. Other studies have reported MAS to produce similar effects to CPAP on some neuropsychological measures [23, 25, 26], but not others [23, 25]. Quality of life, measured by validated questionnaire, is also improved with MAS compared to placebo tablet [25].

The potential to modify cardiovascular outcomes is an important goal of any treatment for OSA as the disorder is associated with increased risk of cardiovascular morbidity and mortality. Modest reductions in blood pressure following MAS treatment have been reported in uncontrolled studies [29, 30]. Two randomized placebo-controlled trials, using intention to treat analyses, have also reported a blood pressure reduction of similar magnitude (2–4 mmHg) after MAS treatment for periods of 1 and 3 months [18, 25]. The effect of MAS treatment in regards to cardiovascular endpoints, such as cardiovascular events and mortality, are yet to be investigated. However, indications that there may be a positive impact have been shown in studies investigating intermediate endpoints. One study has shown improvement in oxidative stress and endothelial function after 1 year of MAS treatment



for OSA [31]. A subsequent investigation has shown improved endothelial function after 2 months of MAS treatment, to the same extent as that seen with CPAP in this crossover study [32].

### ***Long-Term Efficacy***

Less is known about the efficacy and effectiveness of MAS therapy long term. However, studies reevaluating patients between 1 and 5 years after initiation of treatment indicate a reasonably high rate of sustained control of OSA [21, 33, 34]. The main reasons for relapse can be attributed to appliance failure due to wear and tear, with patients who have replaced or adjusted their appliance faring better long term [33]. Weight gain may over time also decrease efficacy [35] and these issues highlight the need for long-term dental and medical follow-up.

### ***Effectiveness Compared with Other Treatments***

As the current gold standard for OSA treatment, CPAP is highly efficacious and cross-over trials comparing MAS to CPAP consistently find that MAS is less efficacious in improving the polysomnographic measures of OSA [25, 26, 36, 37]. However, although CPAP is superior in reducing AHI and improving oxygen saturation, similar improvements in health outcomes suggest MAS may not be inferior to CPAP in clinical practice. For example, several randomized controlled trials have reported similar reductions in blood pressure despite inferiority of MAS in normalizing polysomnographic indices [25, 38]. Although CPAP is highly efficacious, tolerance and adherence are often low and it is known that patient preference generally lies in favor of oral appliances. This raises the possibility that the superior efficacy of CPAP is mitigated by inferior compliance, resulting in MAS and CPAP having overall similar effectiveness in the clinical setting. A summary of published randomized cross-over studies of CPAP vs. MAS is shown in Table 9.1.

TRD are used less commonly than MAS and investigations into their efficacy as a treatment for OSA remain limited [4, 22, 39, 40]. A recent randomized cross-over study comparing MAS and TSD found similar reductions in AHI with both appliances; however, patient tolerance and subjective compliance was less with TRD and patient preference favored MAS [22]. The focus of the remainder of this chapter will be MAS as TRD are rarely used in clinical practice.

Comparisons of surgical treatments for OSA are sparse. A randomized trial comparing MAS with surgical treatment (uvulopalatopharyngoplasty) found that MAS had higher success rates in improving OSA and this greater effectiveness of MAS in AHI reduction was evident at both 1 and 5 years follow-up [34].

Table 9.1 Efficacy of MAS vs. CPAP: summary of published randomized crossover studies

Study (first author, year)	Study recruitment		Treatment interval	Treatment efficacy					Treatment preference
	Inclusion criteria			AHI (h)	CPAP	AHI (h)	MAS	P value MAS vs. CPAP	
	AHI (h)	No. (% males)							
Clark, 1996 [65]	≥15	23 (100%)	2 weeks	38.9 ± 14.3	11.2 ± 3.9 <sup>a</sup>	19.9 ± 12.7 <sup>a</sup>	N/A	MAS	
Ferguson, 1996 [66]	15–50	27 (89%)	4 months	19.7 ± 13.8	3.5 ± 1.6 <sup>a</sup>	9.7 ± 7.3 <sup>a</sup>	<0.05	MAS	
Ferguson, 1997 [66]	15–55	24 (79%)	4 months	25.3 ± 15.0	4.0 ± 2.2 <sup>a</sup>	14.2 ± 14.7 <sup>a</sup>	<0.05	MAS	
Engleman, 2002 [26]	≥5	51 (76%)	8 weeks	31 ± 26	8 ± 6 <sup>a</sup>	15 ± 16 <sup>a</sup>	<0.01	CPAP	
Randerath, 2002 [36]	5–30	20 (80%)	6 weeks	17.5 ± 7.7	3.2 ± 2.9 <sup>a</sup>	13.8 ± 11.1 <sup>a</sup>	<0.01	MAS	
Tan, 2002 [37]	<50	24 (83%)	2 months	22.2 ± 9.6	3.1 ± 2.8 <sup>a</sup>	13.8 ± 11.1 <sup>a</sup>	NS	MAS	
Barnes, 2004 [25]	5–30	104 (80%)	3 months	21.3 ± 1.3	4.8 ± 0.5 <sup>a</sup>	14.0 ± 1.1 <sup>a</sup>	<0.05	CPAP	
Hoekema, 2008 [67]	≥5	103 (89%)	2–3 months	39 ± 4.3	2.4 ± 4.2 <sup>a</sup>	7.8 ± 14.4 <sup>a</sup>	NS	N/A	
Gagnadoux, 2009 [23]	10–60	59 (78%)	8 weeks	34 ± 13	2 (1–8)	6 (1–8)	<0.001	MAS	

AHI values = Mean ± SD except Gagnadoux, 2009 = median (interquartile range)

<sup>a</sup> *p* < 0.05 compared to baseline

## Patient Selection and Prediction of Treatment Outcome

### *Indications for Treatment*

In 2006 the American Academy of Sleep Medicine (AASM) published an update to their clinical practice parameters for the use of oral appliances for the treatment of OSA [2]. These parameters state that oral appliances are indicated for patients with mild to moderate OSA who prefer an oral appliance over CPAP, or in those who are do not respond to CPAP, are not appropriate candidates for CPAP, or who fail treatment attempts with either CPAP or behavioral measures (e.g., weight loss or positional therapy). It is recommended that patients with severe OSA initially trial CPAP before considering oral appliance treatment based on the superior efficacy of CPAP.

### *Oral Considerations*

Dental considerations are the initial limiting factor in patient selection for MAS treatment. Patients must have enough teeth to permit adequate retention of the appliance, not have temporomandibular joint problems and have sufficient dental health. The use of an oral appliance may result in excessive tooth movement which is an issue in periodontal disease. Also partial denture patients may experience loosening of their dentures due to tooth movements induced by the splint. Although the evidence is not strong, it has been suggested that limited mandibular protrusion (<6 mm) is also a contraindication. One study has suggested that up to a third of patients are excluded on the basis of these dental factors [41].

### *Indicators of Treatment Success*

Beyond the initial dental requirements, patient selection criteria are not necessarily straightforward. A number of factors have been associated with treatment success and are summarized in Table 9.2.

Firstly information from diagnostic sleep studies may aid in patient selection. There is a general belief that increasing OSA severity is associated with treatment failure, although notable exceptions do exist [7, 8]. It has also been reported that MAS has a greater effect on supine compared to lateral AHI and therefore may be more effective in patients with positional OSA [35, 42]. Studies have reported a better treatment response with younger age, lower body mass index, and smaller neck circumference [7, 35]. Female gender has also been suggested to be favorable for treatment success [35]; however, this has not been adequately addressed with prediction studies conducted in predominantly male samples.

Craniofacial factors may be related to treatment response with imaging studies reporting cephalometric variables such as a longer maxilla, smaller overjet, shorter soft palate, distance between mandibular plane and hyoid bone, retropalatal airway

**Table 9.2** Predictors of favorable outcome with MAS treatment

Demographic/anthropometric	Polysomnographic
<ul style="list-style-type: none"> <li>• Younger age</li> <li>• Female gender</li> <li>• Lower BMI</li> <li>• Smaller neck circumference</li> </ul>	<ul style="list-style-type: none"> <li>• Lower baseline AHI</li> <li>• Supine-dependent OSA</li> </ul>
Physiological	Cephalometric
<ul style="list-style-type: none"> <li>• Oropharyngeal collapse</li> <li>• Lower nasal resistance</li> <li>• Airway patency during Müller maneuver following mandibular advancement</li> </ul>	<ul style="list-style-type: none"> <li>• Smaller airway space</li> <li>• Shorter soft palate</li> <li>• Greater distance between hyoid and mandibular plane</li> <li>• Narrower SNB angle</li> <li>• Wider SNA angle</li> </ul>

space and facial height as relating to a positive outcome [7, 43, 44]. Additionally, functional characteristics of the upper airway may be associated with MAS treatment response. Patients who primarily collapse their upper airway in the oropharyngeal region during sleep are more likely to be MAS responders compared to patients displaying primary velopharyngeal airway collapse [45]. OSA patients with lower nasal resistance may also respond more favorably to MAS therapy [46].

Research studies collectively suggest that treatment outcome relates to anthropometric, polysomnographic, physiologic, and anatomical characteristics. However, these potential predictive factors of MAS treatment success have generally not been assessed in prospective studies. Therefore, there is still considerable doubt about the validity and utility of using these factors to aid in patient selection in the clinical practice setting.

### *Techniques for Predicting Outcome*

A consistent finding of all MAS efficacy studies is that not all patients will respond to this form of treatment. There is significant wastage of health resources associated with implementing this form of therapy in patients who will ultimately not experience any clinical benefit. The ability to prospectively identify which patients are likely to respond to MAS therapy is therefore of key importance. Various imaging and physiological techniques have been employed in research studies to identify anatomical and functional characteristics associated with MAS treatment outcome.

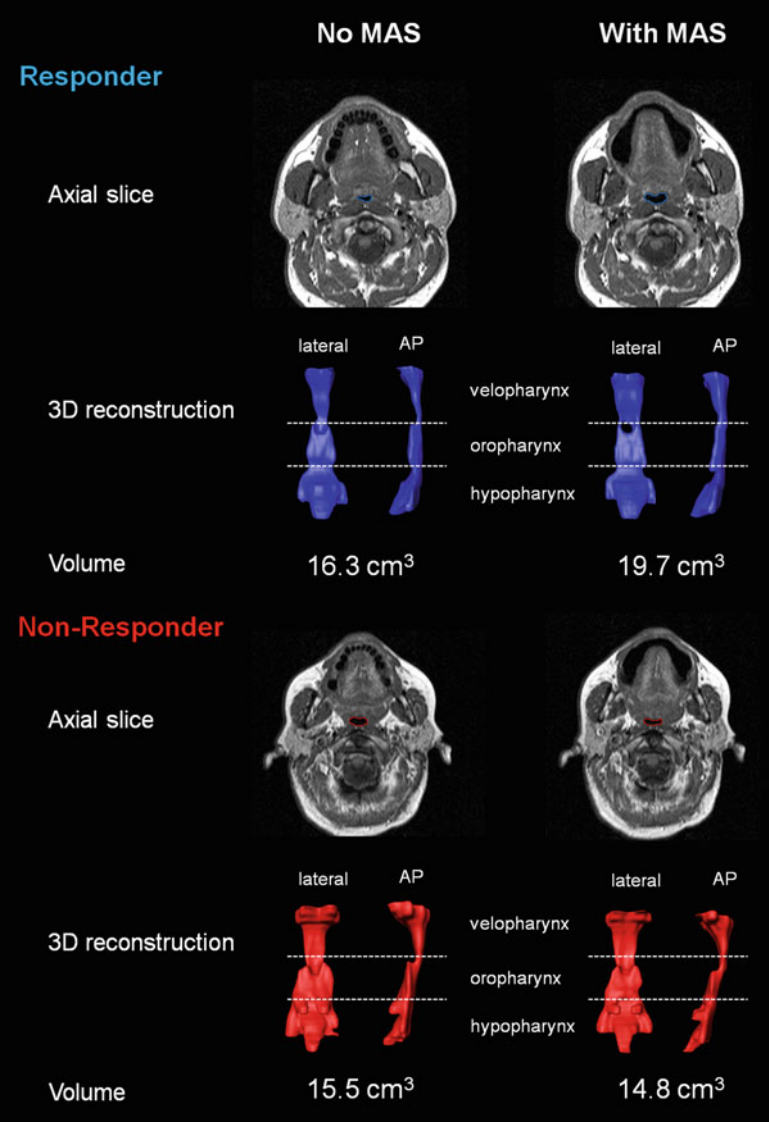
Investigations during sleep have identified primary oropharyngeal collapse, measured by a multisensor pharyngeal catheter, as a highly predictive of treatment success [6]. Nasopharyngoscopy during drug-induced sleep showed improved airway patency with simulated mandibular advancement to be indicative of treatment success [47]. However, such assessments during sleep are generally not feasible to perform in clinical practice. A study comparing polysomnographic outcomes of a thermoplastic “boil and bite” appliance to a custom-made and fitted appliance has found that treatment

response with the less-efficacious disposable appliance could not be used to predict response to the customized appliance [3]. However, single-night titration protocols (see *appliance titration protocols*) may have some predictive utility.

Three-dimensional imaging modalities have been used to view the effects of mandibular advancement on the upper airway during wakefulness. Ultra-fast MRI has demonstrated persistence of airway collapse with mandibular advancement during the Müller maneuver to be indicative of treatment failure [48]. MAS treatment responders also appear to have larger dimensional increases in the upper airway with mandibular advancement in static MR images, compared to nonresponders, particularly in the lateral diameter of the velopharynx (Fig. 9.2) [10].

In the clinical setting, prediction techniques must be simple, widely available, and cost-effective. Expensive assessments must be balanced against the cost of simply constructing an appliance to observe the outcome. Lateral cephalometric radiographs can provide information about craniofacial morphology which may be relevant to MAS treatment outcome. However, 3D imaging studies suggest airway changes in the lateral dimension are most pertinent to MAS treatment response which may limit the predictive utility of lateral cephalometry. Nasopharyngoscopy allows evaluation of changes in airway caliber and real-time imaging additionally facilitates evaluation of airway functional properties (e.g., compliance). In a nasopharyngoscopic study during wakefulness [9] a greater increase in velopharyngeal cross-sectional area during the Müller maneuver was demonstrated in responders compared to nonresponders with mandibular advancement. Awake nasal resistance has also been found to be lower in MAS responders; however, overlapping values between treatment response groups exclude determination of a reliable cut-off value for use in individual patients [46]. Flow-volume curves (obtained by standard spirometry) have been identified as a surrogate marker for the site of upper airway collapse during sleep [49]. A study of 54 OSA patients undergoing oral appliance treatment demonstrated a significantly lower inspiratory flow rate at 50% of vital capacity ( $MIF_{50}$ ) and higher expiratory flow rate at 50% of vital capacity ( $MEF_{50}$ )/ $MIF_{50}$  ratio in responders compared to nonresponders and derived cut-off values had a sensitivity of 91% and specificity of 88% in predicting treatment success.

There is still a long way to go in the development of accurate and reliable prediction techniques before introduction into routine clinical practice. Prediction techniques must be prospectively validated before recommendation for clinical use and this is generally lacking for most MAS prediction models proposed in the literature. A prospective validation study of the flow-volume loop prediction method was undertaken in 35 newly diagnosed OSA patients before commencing MAS treatment [50]. In this prospective study only 48.6% of patients were correctly classified using the previously derived cut-off values. It is likely that the degraded performance of the prediction model is a reflection of the complex multifactorial nature of the upper airway response to MAS treatment. It may be that a single structural or functional assessment is inadequate, especially considering that the relative importance of these factors to treatment outcome is likely to vary between individuals. It may prove that a combination of structural and functional assessments is needed to accurately predict MAS treatment outcome in individual patients.



**Fig. 9.2** Magnetic resonance imaging comparison of the upper airway with and without MAS in a treatment responder and nonresponder. An increase in airway cross-sectional area with MAS can be seen in the axial slice of a MAS treatment responder (posttreatment AHI <5/h). The responder shows an increase in total upper airway volume with MAS compared to without MAS. The most significant changes are in velopharynx and in the lateral, rather than the anteroposterior (AP) dimension. Upper airway analysis of a nonresponder (<50% reduction in posttreatment AHI) shows no increase in upper airway dimensions and, in fact, a slight decrease in upper airway volume occurs when the MAS is in place in this particular patient

## ***Contraindications***

Oral appliances have no known role in treating central sleep apnea or hypoventilation syndromes and therefore should be reserved solely for the treatment of OSA. CPAP should be preferentially implemented in cases where urgent treatment is required to control severe symptoms (such as sleepiness whilst driving) or medical comorbidities because of the extended acclimatization period required for oral appliance therapy.

## **Appliance Titration Protocols**

Determining the amount of mandibular advancement needed to prevent occurrence of apneas and hypopneas is not straightforward as there does not always appear to be a direct correlation between degree of protrusion and therapeutic efficacy. The level of mandibular advancement that is optimally efficacious is likely to depend on the specific pathophysiological traits which predispose the individual to OSA in the first place. Therefore, factors such as craniofacial morphology and upper airway structure and function may influence the therapeutic “dose” of mandibular protrusion that is required. Optimal advancement therefore varies considerably from patient to patient, analogous to individual pressure requirements for CPAP users. However, greater levels of advancement generally appear to be more efficacious [24, 51] and therefore advancement to the maximum limit which the patient can be comfortably tolerated would seem most appropriate. Reported levels of clinically efficacious advancement are in the range of 50–90% of maximum voluntary protrusion [7, 8, 18, 19].

Patient tolerance to MAS increases with wear. Therefore, titratable appliances, which allow incremental advancements over time, offer a clear advantage in their ability to accommodate such adaptation. The standard approach to implementation of MAS is an initial 4-week period of acclimatization followed by an additional 8–12 weeks in which the appliance is incrementally titrated. Although this process optimizes therapeutic benefit, the associated time delay is inappropriate for patients who require rapid treatment (e.g., those who are severely symptomatic or have cardiovascular co-morbidities). In such cases CPAP, which can be implemented immediately, would be the preferred treatment option.

Although titration generally occurs systematically under the direction of a dentist, some studies have assessed patient self-titration protocols. In these cases, patients were either able to adjust their own appliance at home guided by subjective symptom assessment vs. comfort levels [52] or increments were only made beyond the initial advancement level (70–80% of maximum) at the patient’s request [53]. Treatment efficacy in these studies was in accordance with levels seen in those using full titration protocols. Such methods have the potential to reduce the number of time-consuming titration visits which may be a deterrent to some patients in accepting this form of therapy. Assessment of the efficacy of home-titrated advancement by

polysomnography showed that of the patients successfully treated with MAS, 79% were treated at their self-titration level without need for further advancement [52].

Recently, several studies have emerged which explore single-night titration protocols to determine the degree of mandibular advancement which best eliminates respiratory events [23, 54, 55]. The method consists of fitting the patient with a temporary oral appliance which is attached to a hydraulic or motorized advancement mechanism to protrude the lower plate. The degree of advancement can then be controlled remotely via a computer interface without waking the patient. The possibility of single-night titration is highly attractive in that there is the potential to immediately ascertain the extent of therapeutic benefit to a patient, as well as the degree of protrusion needed to achieve this. However, a limitation of this approach may be that without the gradual build-up of tolerance, the required “dose” of mandibular advancement may not be achievable within a single night without subjecting the patient to discomfort.

## Adverse Effects

MAS improve OSA through the changes in airway configuration caused by passively holding the mandible in a more anterior position. By nature, moving the mandible forward via an intra-oral appliance exerts reciprocal forces on the teeth and jaw, and may also apply pressure on the gums and oral mucosa depending on the appliance design. These mechanical effects can result in acute symptoms, as well as long-term dental and skeletal changes. Side effects and complications can occur at any stage during treatment and are generally thought to be minor in nature, although more severe and continuing side effects can lead to cessation of appliance use. Common adverse effects of oral appliance therapy are summarized in Table 9.3.

Side effects are common at the initiation of treatment and during the acclimatization period as would be expected. However, these are generally described as mild and temporary and only occasional lead to discontinuation of use of the appliance. The most commonly reported adverse effects are excessive salivation, mouth dryness, tooth pain, gum irritation, headaches, temporomandibular joint discomfort, and morning after occlusal changes. A pooled side-effect profile from multiple studies suggests 6–86% of patients will experience at least one of these side effects [14]. Differences in the reported incidences of short-term adverse effects probably relates to differences in the appliance used, degree of mandibular advancement, frequency and duration of follow-up, and the expertise of the dentist involved in these studies. Early recognition and attention to such adverse symptoms are important as they have the potential to influence the patient’s ultimate acceptance of the treatment. Resolution of symptoms usually occurs within several days to several weeks with regular use and occasional adjustment of the appliance for fit [15].

More severe and continuing adverse symptoms include temporomandibular joint pain, myofascial pain, tooth and gum pain, dry mouth, and salivation [14]. Observations from collective studies place the occurrence of on-going effects in the



**Table 9.3** Adverse effects associated with MAS use

Short-term	Long-term
<ul style="list-style-type: none"> <li>• Dental discomfort (especially upper and lower incisors)</li> <li>• Temporomandibular joint pain</li> <li>• Mouth dryness</li> <li>• Salivation</li> <li>• Gum irritation</li> <li>• Bruxism</li> </ul>	<ul style="list-style-type: none"> <li>• Occlusal changes</li> <li>• Increased facial height</li> <li>• Increased mouth opening</li> <li>• Increased mandibular plane angle</li> <li>• Changes in inclination of incisors</li> </ul>

range of 0–75%, but again, differences in oral appliances design and implementation may account for the varying rates. These symptoms may occasionally lead to discontinuation of use of the appliance.

Dental and skeletal changes are evident with long-term use of MAS. Data now exists from studies which have monitored patients up to 7 years after initiation of MAS therapy. Changes in occlusal contact area have been identified with long-term use [56] and increased facial height, mouth opening, and changes in the inclination of the incisors have also been reported [57–59]. Duration of wear of the oral appliance tends to correlate with the extent of changes in the bite relationship and mandibular posture [60, 61]. However, favorable occlusive changes have been reported in 41% of patients, with some patients showing no change at all (14%) [60]. Orthodontic changes and the desirability of such changes may be predicted on the basis of pretreatment dental characteristics [60, 62]. For example, a greater overbite at baseline has been reported to be associated with both smaller and more favorable orthodontic changes. The influence of different device designs on occlusal relationships has not been thoroughly investigated; however, a soft elastomeric device has been shown to induce smaller effects compared to a hard acrylic device [62]. Generally, these changes are minor or even subclinical and it is uncommon that it will be necessary to cease treatment on this basis. However, should significant occlusal changes occur, the decision to discontinue this form of therapy should be weighed against the degree of this change, the severity of OSA and the feasibility of treatment alternatives such as CPAP.

Preliminary evidence from a small randomized controlled trial suggests daily jaw exercises improve occlusal contact area and bite force. Such exercises may relieve masticatory muscle stiffness and facilitate movement of the mandible to its normal position and therefore be a potential method to help minimize occlusal changes in predisposed patients [63].

## Treatment Adherence

Adherence to oral appliance treatment depends on the balance between the perceived benefit of treatment vs. the side effects experienced. A variety of factors can influence tolerance particularly during the initiation of therapy, and these include adequate

communication, initial frequent monitoring, and appropriate design and fit of the appliance for the individual. Patients need to be fully informed of the possible discomfort and the importance of the acclimatization period.

Unlike CPAP compliance, which can be objectively monitored via download of usage data from the machine, there is currently no commercially available method for objectively measuring MAS adherence in clinical practice. Therefore, most compliance data in the literature are based on self-report. A summation of subjective compliance data from multiple studies suggests on average 77% of patients still use the appliance at 1 year [14]. One study has employed a novel intra-oral device which utilizes embedded temperature sensors to objectively monitor compliance [64]. Data indicated that on average patients used the appliance for 6.8 h per night (with a range of 5.6–7.5 h) which is similar to figures from studies using subjective reports. As greater MAS compliance rates relative to CPAP are likely to be a factor equilibrating health outcomes between the two treatments, there is a need for technological advances and studies to objectively evaluate this issue.

## Interdisciplinary Care Model

As MAS is a dental-based treatment for a medical sleep disorder, a multidisciplinary care approach is necessary. A sleep physician and dental practitioner with expertise in the management of sleep disordered breathing are required to effectively implement oral appliance therapy for OSA and enhance patient outcomes. Therefore, communication between disciplines and planning along a coordinated treatment pathway that is also accessible to and understood by patients is integral to successful outcomes. It is recommended that the therapeutic efficacy of oral appliance therapy is objectively assessed in all patients by polysomnography or an attended cardio-respiratory (Type 3) sleep study with the oral appliance in place after final adjustments of fit have been made. This is based on reported associations of even mild OSA with adverse health outcomes, especially in patients with comorbid disease or risk factors and additionally, that some patients are known to experience an increase in AHI while using an oral appliance. Ongoing review and care in both medical and dental settings is required to assess compliance, comfort, and fit of the device as well as monitoring of treatment efficacy and side effects.

## Future Research

Although a role for oral appliances in the treatment of OSA is now well established, there are still key unresolved issues that need to be addressed by future research.

- *Prediction methods for patient selection.* The current lack of a valid and reliable prediction method for treatment outcome represents a major barrier to the widespread adoption of this treatment modality in clinical practice. It is hoped that

ongoing research will identify patient subgroups with greater likelihood of treatment success. The most accurate prediction method may incorporate several functional and structural assessments from an individual patient into an overall prediction model.

- *Objective compliance monitoring.* The development of technologies that can objectively monitor nightly oral appliance use, as can be done with CPAP, will be essential in research and clinical practice.
- *Influence of different appliances and designs.* The influence of different appliance design on treatment outcome and side effects is not clear. Comparative studies are essential to define the design features that optimize outcomes.
- *Simplification of titration procedures.* Current titration procedures require significant time to reach the point of optimal treatment efficacy and represent a significant barrier to implementation of this therapy particularly in symptomatic patients. Single-night titration protocols may offer hope in this regard.
- *Clinical effectiveness for modifying adverse health outcomes of OSA.* Although recent studies leave little doubt about the short-term efficacy of oral appliances, there is a need for long-term follow-up studies, particularly in regard to the effects of MAS on the health consequences of OSA. The clinical effectiveness of MAS in modifying these factors also needs to be compared with CPAP.
- *Long-term efficacy and adverse effects.* As OSA is often a lifelong condition, treatment needs to be effective long term. There is a need for longitudinal studies of efficacy and the factors affecting this, as well as potential adverse effects.

## Conclusion

Oral appliances are increasingly being used to treat OSA. MAS are the most common type of appliance used in clinical practice. Robust evidence of the efficacy of oral appliances for improving polysomnographic indices and modifying health risks associated with OSA has emerged over the last decade. Although CPAP has greater overall efficacy compared to MAS, patients generally prefer MAS and therefore differences in adherence profiles between the two treatments may level their efficacy in clinical practice. Side effects such as excessive salivation, muscle and tooth discomfort are common during the initial treatment stages but are most often minor and abate with continued use. Longer term effects of MAS wear, such as tooth movement and malocclusion, occur in a significant number of patients but are usually minor in nature and do not require cessation of treatment.

## Summary of Keypoints

- Oral appliances are increasingly being used for the treatment of OSA with the most common appliance type being those which hold the mandible in a protruded position (MAS).

- Although individual appliance designs vary, the advancement of the mandible is key to their effectiveness in reducing upper airway collapsibility during sleep.
- Oral appliances can be effective in treating a range of OSA severities with around two-thirds of patients achieving a clinically important response and complete resolution of OSA (AHI reduced  $<5/h$ ) occurring in around 40% of patients.
- Although oral appliances are less efficacious in reducing polysomnographic indices of OSA compared to CPAP similar improvements in health outcomes suggest that the superiority of CPAP in improving oxygen desaturations and AHI may be mitigated by inferior compliance, resulting in both treatments having overall similar effectiveness in the clinical setting.
- Various factors have been associated with greater likelihood of treatment success such as female gender, younger age, supine-dependent OSA, lower BMI, smaller neck circumference, and craniofacial factors.
- Short-term side effects (such as discomfort and excessive salivation) are common but usually minor and transient and long-term dental changes appear to be generally minor.
- Long-term side effects include tooth movements, although only occasionally warranting cessation of therapy. Patients should be informed of this possibility before embarking on treatment.
- As oral appliances are a dental-based treatment for a medical sleep disorder, a multidisciplinary care approach is necessary. Collaboration between sleep physicians and dental practitioners, for diagnosis and treatment is recommended to effectively implement oral appliance therapy for OSA and enhance patient outcomes.

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# Chapter 10

## Obstructive Sleep Apnea: Surgery

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**Keywords** Obstructive sleep apnea • Positive airway pressure therapy • Airway reconstructive surgery • Uvulopalatopharyngoplasty • Sleep disorders • Snoring • Nasal surgery • Allergic rhinitis • Expansion sphincter pharyngoplasty • Transpalatal advancement surgery • Hypopharyngeal surgery • Maxillomandibular advancement surgery

### Introduction

Obstructive sleep apnea (OSA) is, for most patients, a chronic condition that will require management across the lifespan. Like most chronic diseases, *prevention* of OSA remains the ideal and most attractive treatment from a public health perspective. At this juncture, however, *management* of the large population of patients diagnosed with sleep-related breathing disorders (as well as those who are still undiagnosed), remains the critical focus of most sleep physicians. As with hypertension, diabetes, and other chronic conditions, the individual treatment plan is not aimed at “cure,” but rather (1) symptom and quality of life improvement and (2) reduction of cardiovascular and general health risk.

Both physician and patient understanding of OSA in this context is the cornerstone for successful management. This approach allows for customization of each

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individual's treatment plan depending on their symptoms, airway anatomy, disease severity, and medical comorbidities. Across the lifespan, the same patient, with the same AHI, may benefit from different treatment options, or a combination of treatment options, depending on the clinical context at that particular stage of life. It is imperative to treat the patient, not just the AHI.

In its simplest form, OSA is characterized by an upper airway that is too narrow and/or too collapsible. As such, upper airway reconstructive surgery certainly can and should play a role in the treatment of patients with this upper airway disease, particularly those who fail treatment with other medical device therapies. Proper management of OSA in the twenty-first century requires the ability to obtain a proper sleep history, to thoroughly examine each individual's unique airway anatomy, and to be at least familiar with a variety of both medical and surgical treatment options. Positive airway pressure (PAP) therapy remains the most attractive first-line treatment and an excellent long-term management strategy for many patients given its effectiveness, low morbidity, and reversibility. Acceptance and long-term compliance rates with PAP therapy are suboptimal, particularly in certain subgroups such as patients who are younger, not sleepy, have milder disease, and/or have symptomatic nasal obstruction. Without other treatment options, millions of OSA patients will continue to suffer from the symptoms and cardiovascular morbidity associated with this disease.

The aim of this chapter is to provide the sleep medicine practitioner with a general overview of the approach to the sleep patient from a surgical/anatomical perspective with discussions on the importance of examining the upper airway, recognizing different airway phenotypes, and understanding the role of upper airway reconstructive surgery with its unique challenges and future directions; rather than providing a list of available surgical techniques, which often vary by surgeon/region and are currently rapidly evolving.

## **Clinical Evaluation**

### ***Background and Clinical Context of Surgical Therapy***

Device treatments, such as PAP therapy or an oral appliance, are critically dependent on regular continued daily application to replicate the results recorded in the very limited time observed in the sleep laboratory setting. One must be cautious when translating the reduction of the AHI and improvement of other objective sleep measures with PAP therapy on a couple of hours of sleep on a therapeutic polysomnogram into real-life clinical efficacy, although data management software is available that allows clinicians to assess longitudinal control of the AHI. It is still unclear what the effect of partial usage is on long-term reduction of cardiovascular risk and what level of device compliance is necessary to achieve acceptable disease management [1].

Surgical therapy differs in this regard, in that it does not depend on usage or compliance. In fact, it is this aspect that is often attractive to patients. Nevertheless,

surgery presents its own challenges in determining what defines successful management. The nature of surgical therapy lends itself to judgment by AHI criteria before and after the surgical intervention – a measurement that often poorly reflects the actual clinical outcome and whether the goals of surgical therapy were achieved. For research purposes, arbitrary AHI criteria have been used to define adequate surgical therapy, for example, AHI <20 with at least a 50% reduction in the AHI [2]. The specific improvement in PSG criteria necessary for symptom improvement and reduction of cardiovascular risk is still largely unknown and likely varies greatly from patient to patient. Unfortunately, despite its past use as the primary marker of surgical success, the AHI is only one metric of disease severity and overall correlates poorly with patient symptoms, general health and sleep-related quality of life measures, and performance on psychomotor vigilance testing [3].

The following patient examples below illustrate this point, and a glimpse of the much larger problem of determining what defines successful surgical management.

1. Patient 1 undergoes surgical therapy for severe OSA, and has an AHI reduction from 100 to 24. Postoperatively he has resolution of his loud snoring, nocturnal awakenings, and daytime sleepiness. His blood pressure is also under better control with less medication.
2. Patient 2 undergoes surgical therapy for moderate OSA, and has an AHI reduction from 29 to 14. Postoperatively he complains of persistent snoring and excessive daytime sleepiness.

By historical measures of surgical “success,” the problem with evaluating AHI alone is quite clear, where Patient 1 would be considered a treatment failure while Patient 2 is documented as treatment success. Although the exact criteria for delineating successful management of patients with sleep apnea is still unknown, the inadequacy of AHI analysis alone must be recognized.

Evaluating the effectiveness of surgical therapy is further complicated by the wide variety of procedures and different surgical techniques available, as well as the ethical and practical concerns with instituting randomized controlled sham-procedure studies. Nevertheless, it is clear that airway reconstructive surgery has benefits in many patients with OSA. A recent large Veterans Administration (VA) population study showed a 31% reduced mortality rate in OSA patients treated with uvulopalatopharyngoplasty (UPPP) compared to those treated with CPAP, even after controlling for medical comorbidities and other clinical factors [4]. In no way does this suggest that UPPP is more effective than CPAP; rather, it suggests that, across a population, reduction in disease severity with surgical therapy may be as effective in improving quality of life and overall morbidity as a medical therapy device with significant non-adherence concerns.

## ***Role of Surgical Therapy***

For the millions of patients who will not accept or cannot tolerate PAP therapy or who have compliance rates that are suboptimal for clinical success, surgical therapy

can provide a method of symptom and quality of life improvement in addition to a reduction in cardiovascular risk. Besides sole therapy, surgery also can play an effective role as part of combination therapy and an adjunct to medical treatment. For example, as referenced later, surgical treatment of symptomatic nasal obstruction can reduce PAP pressure requirements, improve PAP compliance, and improve tolerance of an oral appliance.

The surgical treatment of OSA has evolved rapidly over the last decade. Better understanding of the pathophysiology of OSA and improved methods of airway evaluation, such as sleep endoscopy, and a better understanding of patterns of obstruction have led to new surgical approaches. In the past, patients intolerant to PAP therapy were typically offered traditional palatal surgery with relatively poor overall success rates. Those who failed to improve were then offered more morbid but potentially more effective skeletal surgery. The current paradigm avoids this “cookie-cutter” approach and instead relies on specifically identifying and treating each individual’s unique pattern of airway obstruction. New evidence-based techniques with improved results, lower morbidity, and faster recovery are now available and are quickly relegating the traditional UPPP and rudimentary methodology to the historical archives.

### ***Patient Evaluation***

In order to improve surgical success, it is important to first analyze cases of surgical failure. One major contributor to persistent symptoms after surgical therapy is the failure of identifying comorbid sleep disorders. Approximately one third of patients with OSA have another sleep disorder that may be causing or at least contributing to the patient’s symptoms [5]. A patient whose excessive daytime sleepiness is primarily related to restless legs syndrome, as opposed to the patient’s OSA, will clearly have no chance of successful symptomatic improvement with airway surgery. Therefore, a comprehensive sleep history and evaluation for other confounding sleep pathology is critical to managing OSA patients effectively.

Diagnostic failure can also take the form of inadequate examination of the airway and identification of the specific anatomical concerns. The problem with sleep apnea is not one of “stenosis” or “site of obstruction.” Instead the upper airway is a physiologic tube with properties of size, shape, compliance, and length, best modeled in the form of a Starling resistor [6, 7]. It is not simply the *level* of obstruction that counts; but rather, the specific *structure*, *anatomy*, and *pattern* of obstruction that drives proper surgical procedure selection. Just because a patient with clear palatal obstruction undergoes a palatal procedure, does not necessarily ensure that the patient’s palatal obstruction was adequately addressed. Successful surgical therapy is critically dependent on knowledge of the airway anatomy and physiology.

A number of diagnostic tools are available to assist the surgeon in preoperative upper airway evaluation and to guide surgical planning [8]. Radiographic techniques include lateral cephalometric X-ray, computed tomography (CT) scan, and

cine-magnetic resonance imaging (cine-MRI). Cephalometric X-rays are the most commonly used radiographic tool. They are particularly useful for analyzing craniofacial anatomy and preparing for skeletal surgery. The information is limited, however, in that the images are usually obtained while the patient is awake and upright and do not provide dynamic visualization of the soft tissue anatomy and airway physiology. Sleep MRI is an emerging technology that addresses some of these limitations although cost and machine noise effects on sleep are barriers to widespread adoption of this tool.

Direct visualization techniques include head and neck physical examination, flexible nasolaryngoscopy, and drug-induced sleep endoscopy (DISE). Physical examination is essential to patient evaluation and generally quick and inexpensive to perform. DISE allows for dynamic examination of the airway during conditions that mimic the low airway muscle tone of sleep [9]. When performed under specific conditions and guidelines, propofol-induced sleep correlates most closely with deeper levels (stage N2) of NREM sleep and maintains a similar AHI as compared to physiologic sleep [10]. Studies of sleep endoscopy have demonstrated validity, test–retest reliability, and inter-rater reliability [11, 12]. Recent data suggests that utilization of DISE can improve treatment outcomes with oral appliances [13–15].

## Snoring

On the spectrum of sleep-related breathing disorders, non-apneic snoring is a very common condition. Snoring is often the chief complaint of patients and subjectively more important to most patients than daytime sleepiness, regardless of the AHI [16]. Snoring has been shown to disrupt bed-partner sleep and have negative impact on marital relationships. Further, treatment of snoring not only improves the *patient's* sleep but has also been documented to improve the *bed-partner's* sleep, with a reduction in the bed-partner's arousal index and improvement in sleep duration and efficiency [17]. In pediatric populations, primary snoring has been directly linked to elevated nocturnal diastolic blood pressure, after controlling for other clinical factors [18].

Recent evidence also suggests that vibratory trauma from snoring may cause direct endothelial injury and may be an independent risk factor for carotid atherosclerosis [19]. Researchers in Australia have developed a rabbit model for evaluating the effects of snoring on the carotid artery. They have concluded that significant vibrational energy is transmitted to the carotid arterial wall during snoring, and may provide a link to carotid atherogenesis and cerebrovascular risk [20, 21].

Some patients with an AHI in the normal range, particularly younger patients, may demonstrate flow limitation, snoring, and increased respiratory effort with a subsequent clinically significant negative impact on their sleep. Many of these patients with a true sleep-related breathing disorder are not offered positive pressure or other forms of medical therapy because of the misdirected sole focus on the AHI alone. Although hundreds of over-the-counter products are available to treat this

condition, known as non-apneic snoring or upper airway resistance syndrome, most do not work, and again potentially more effective medical therapy options such as CPAP are typically either not covered by insurance and/or not tolerated by this subset of patients [22].

In properly selected patients, surgical treatment options, often done under local anesthesia in the outpatient office, can provide excellent results with minimal discomfort, morbidity, and risk. Nasal surgery alone in patients with increased nasal resistance and symptomatic nasal obstruction has been shown to improve snoring, presumably by restoring laminar airflow entering the pharynx and subsequently reducing palatal flutter. Tonsillectomy and/or adenoidectomy, particularly in pediatric patients, can be an attractive first-line treatment option for non-apneic snoring in patients with adenotonsillar hypertrophy. In about 80% of patients with non-apneic snoring, the pathophysiology lies in a palatal flutter mechanism. In patients with palatal flutter, without adenotonsillar hypertrophy or nasal obstruction, a variety of office-based surgical procedures, such as injection snoreplasty, radiofrequency treatment, or palatal implants can provide effective control of snoring and improvement in subjective sleep quality and daytime sleepiness [23–25].

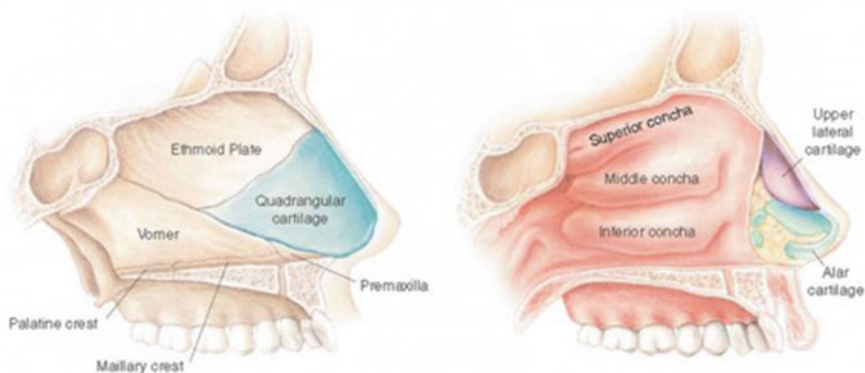
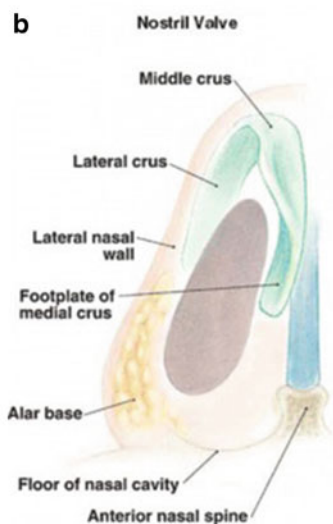
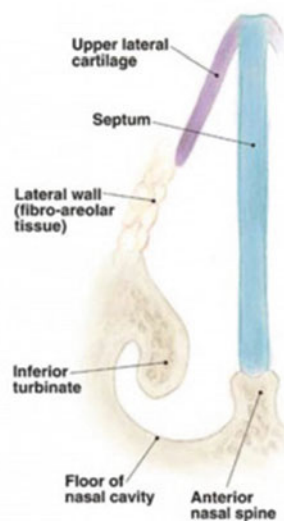
## Nasal Surgery

### *Anatomy and Physiology*

Most otolaryngologists have had patients return to the office after nasal surgery, performed for other non-sleep-related sinonasal problems, only to report that their sleep quality dramatically improved after their nasal surgery. Almost 500 years ago, the Dutch physician, Lemnius [26], provided one of the first documented reports of nasal obstruction and its negative impact on sleep. The literature is abundant with data linking the nasal airway and sleep, although the exact relationship has been rather elusive.

Knowledge of the nasal anatomy (i.e., internal and external nasal valve areas) and the physiology (i.e., autonomic control of venous capacitance vessels) are essential to proper evaluation of the nose as it relates to sleep-disordered breathing (Fig. 10.1). The internal nasal valve, which is bordered by the anterior septum, anterior tip of the inferior turbinate, and the caudal border of the upper lateral cartilage, is the area of highest nasal resistance. This is important for breathing during sleep because nasal resistance accounts for more than half of the total upper airway resistance. Airflow mechanics (Poiseuille's law) dictate that very small changes in cross-sectional radius ( $r$ ) can exponentially affect airflow ( $Q$ ):  $Q = \Delta P \pi r^4 / 8 \mu L$ .

Both structural and inflammatory mechanisms can contribute to increased nasal resistance and subsequent negative impact on sleep (Tables 10.1 and 10.2). Therefore, a wide variety of both medical and surgical management strategies are available depending on each patient's specific pathophysiology. The coronal maxillofacial CT scan shown illustrates a common example of multiple causes of nasal obstruction (Fig. 10.2).

**a****b****c**

**Fig. 10.1** Nasal anatomy: (a) Structural anatomy of the nasal septum (*left*) and lateral nasal wall (*right*); (b) cross-sectional anatomy of the external nasal valve area; and (c) cross-sectional anatomy of the internal nasal valve area, which corresponds to the location of highest nasal airway resistance. Courtesy of Springer images

Tonsillar hypertrophy has been shown to increase nasal resistance and contribute to symptomatic nasal obstruction and mouthbreathing [27].

### ***Allergic Rhinitis and Sleep***

Sleep impairment is very common in patients with allergic rhinitis, chronic rhinosinusitis, and nasal polyposis, and has a significant impact on disease-specific and general health quality of life measures [28]. In fact, sleep disturbance is one of the

**Table 10.1** Medical/inflammatory causes of increased nasal resistance

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Allergic rhinitis
Non-allergic rhinitis
• Vasomotor rhinitis
• Atrophic rhinitis
• Rhinitis medicamentosa
• Non-allergic rhinitis with eosinophilia syndrome (NARES)
• Medications (e.g., antihypertensives, aspirin, oral contraceptives)
• Infection (e.g., common cold, chronic rhinosinusitis)
• Hormonal (e.g., pregnancy, hypothyroidism)
• Autoimmune (e.g., lupus, Wegener's, rheumatoid arthritis)
• Occupational (e.g., chemicals, paint fumes, chalk dust, saw dust, perfumes)
• Smoking

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**Table 10.2** Structural causes of increased nasal resistance

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Common
• Deviated nasal septum
• Inferior turbinate hypertrophy
• Concha bullosa
• Nasal polyps
• Adenoid hypertrophy
• Tonsillar hypertrophy
• Narrow pyriform aperture/hard palate
Uncommon
• Inverting papilloma
• Neoplasm
• Foreign body
• Synechiae
• Meningocele
• Granulomatous disease

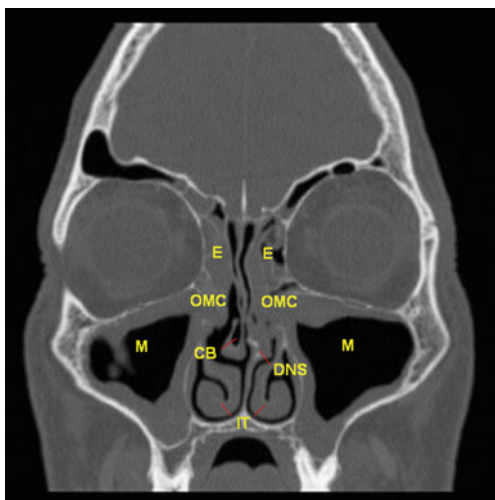
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key factors in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines that distinguishes between mild and moderate–severe disease [29]. Furthermore, the degree of sleep impairment is linearly related to the severity of their sinonasal disease at the time, i.e., patients with predominant tree pollen allergy have noticeable worsening in their sleep during the spring pollen season. In Craig's survey of over 2,000 allergy patients, nasal congestion is the most common complaint and approximately half report difficulty falling or staying asleep [28].

There is a circadian variation to nasal congestion with a predictable worsening overnight in most patients. This physiology is likely multifactorial and attributable to gravity effects of the dependent sleeping position and a decrease in serum cortisol levels overnight. Inflammatory mediators associated with allergic rhinitis demonstrate a circadian rhythm with progressive worsening overnight and peaking in the early morning hours (average ~6:00 a.m.) [28].



**Fig. 10.2** Nasal obstruction: A coronal maxillofacial CT scan shows a deviated nasal septum to the *left* (DNS), inferior turbinate hypertrophy (IT), and a right concha bullosa (CB). This scan also depicts inflammatory changes in the maxillary (M) and ethmoid (E) sinuses and obstruction of the osteomeatal complexes (OMC), often seen with chronic rhinosinusitis



**Table 10.3** Pathophysiologic mechanisms of nasal obstruction and sleep-disordered breathing

- Decreased nasal receptor stimulation
- Increased negative inspiratory pressure in the pharynx
- Increased velocity and turbulence of airflow and palatal flutter
- Shift to oral breathing and posterior displacement of the mandible
- Skeletal changes (chronic)
  - Maxillary hypoplasia
  - Inferior displacement of the mandible
  - Narrowing of dental arches
  - Anterior crossbite
  - Maxillary overjet
  - Increased anterior facial height (elongated face)

### ***Pathophysiology of Nasal Obstruction and Sleep Disturbance***

A number of mechanisms have been proposed to explain how nasal obstruction negatively impacts breathing during sleep (Table 10.3). In 1985, White et al. [30] showed that abolishment of the nasal receptor reflexes with topical lidocaine contributes to an increase in airway obstruction and depression of the central respiratory drive. Other studies confirm that nasal breathing, as opposed to oral breathing, is associated with greater minute ventilation and an increase in pharyngeal muscle activity [31, 32].

Rhesus monkey studies at UCSF in the 1970s elegantly showed that animals with nasal occlusion developed severe craniofacial changes during growth (Table 10.3), all of which have been associated with sleep-disordered breathing in adulthood [33, 34]. It has been hypothesized that a vicious cycle evolves in some patients where nocturnal breathing abnormalities cause unstable oral breathing and secondary



**Table 10.4** Surgical therapy options to treat nasal obstruction

- 
- Septoplasty
  - Inferior turbinate reduction
  - Nasal valve procedures (e.g., spreader grafts, suspension suture)
  - Adenoidectomy
  - Tonsillectomy
  - Nasal polyp removal
  - Concha bullosa resection
  - Lysis of synechia
  - Rapid maxillary expansion
- 

impaired craniofacial growth which then reinforces abnormal breathing. Multiple human studies of nasal occlusion confirm the negative impact on sleep, demonstrating sleep fragmentation, abnormal sleep architecture, and increased respiratory events in patients with nasal obstruction [35–37]

### ***Nasal Obstruction and Sleep-Disordered Breathing***

A number of large population-based studies have analyzed the association of nasal obstruction and subjective sleep measures, snoring, and sleep apnea. In the Wisconsin cohort of almost 5,000 patients, nasal congestion was associated with an increased risk of non-restorative sleep and daytime sleepiness [38]. Several large epidemiologic studies report that nasal congestion is an independent risk factor for snoring [38–40]. Some studies have also shown that, across a large population, nasal obstruction is also an independent risk factor for OSA [39, 41].

### ***Surgical Treatment of Nasal Obstruction***

It is clear that nasal obstruction can have significant negative impact on both subjective and objective sleep measures as well as on the risk of sleep-disordered breathing. Until recently, it has been unclear what effect treatment of the nose has on these parameters. The management approach to the patient generally involves first identifying and medically treating allergic rhinitis or any other inflammatory process that may be present. For structural anatomical problems, surgical therapy can be very effective but the specific procedures indicated may vary from patient to patient and depend on the specific anatomical problem. Although septoplasty and inferior turbinate reduction are most commonly performed in adults, procedure selection must be customized to each individual's anatomical pattern of obstruction (Table 10.4).

An exhaustive description of the specific surgical techniques, pearls, and pitfalls, is beyond the scope of this chapter. More important is an analysis of the results obtained, as they relate to sleep-disordered breathing, by surgically lowering nasal resistance. In 2008, Li et al. [42] showed that, for OSA patients with a deviated nasal septum and symptomatic nasal obstruction, septoplasty lowered nasal resistance, increased mean cross-sectional area, and significantly improved snoring as measured by both the Snore Outcomes Survey and Spouse/Bed Partner Survey. Similar improvement in nasal resistance and snoring was noted by Nakata et al. [27] in 2007 after simple tonsillectomy in patients with 3–4+ tonsils.

Nakata et al. [43] also recently demonstrated that nasal surgery, in the setting of nasal obstruction and sleep apnea, improves nasal resistance, sleep architecture, and daytime sleepiness. In these patients, improvement in the ESS (10.6→4.5) with nasal surgery is comparable to the improvement obtained with other forms of OSA therapy, including positive pressure. In a prospective longitudinal cohort study of patients with nasal obstruction and OSA, nasal surgery also significantly improved both disease-specific and general health (SF-36) quality of life measures [44]. Even in pediatric OSA populations, attention to nasal obstruction is important. Sleep physicians at Stanford recently demonstrated that pediatric patients with enlarged inferior turbinates often had both subjective and PSG evidence of persistent disease after adenotonsillectomy alone [45]. These residual symptoms and AHI elevation were subsequently improved further with the addition of radiofrequency turbinate reduction.

Despite the evidence of the beneficial impact of lower nasal resistance on sleep architecture, sleep efficiency, snoring, daytime sleepiness, and quality of life measures, the importance of treating nasal obstruction has often been overlooked because of its variable and sometimes negligible effect on the AHI. Across large heterogeneous populations, lowering nasal resistance may have little effect on the AHI, which makes sense since it is the pharynx, not the nose, where dynamic airway collapse occurs. However, in selected OSA patients with a normal hypopharyngeal airway, as demonstrated by cephalometrics or physical exam, a clinically significant reduction in the AHI may be achieved. Patient cohorts in which nasal surgery results in successful lowering of the AHI include: small tonsils, low modified Mallampati score, and a normal mandibular plane to hyoid (MP-H) distance on cephalometry. Upper airway exam findings that are associated with a minimal impact on the AHI with nasal surgery alone include: large tonsils, modified Mallampati III/IV, and/or a low hyoid position [46–48].

### ***Nasal Surgery and Improved Effectiveness of Medical Therapy for OSA***

Mounting evidence suggests that increased nasal resistance negatively impacts success rates and tolerance of medical therapy devices, such as CPAP and oral appliances, that are critically dependent upon regular usage to be effective.

With logistic regression analysis, Suguira et al. [49] concluded that increased nasal resistance was one of only two factors associated with non-acceptance of CPAP. In patients with poor CPAP compliance and nasal obstruction, lowering nasal resistance with surgical therapy has been shown to lower average CPAP pressures and improve compliance [50]. Finally, high nasal resistance may negatively impact treatment outcomes in OSA patients treated with mandibular advancement devices [51].

## Oropharyngeal Surgery

### *History*

Most physicians are familiar with the general concept of UPPP. Palatal obstruction has been documented to be at least a contributing factor in most patients with OSA and therefore palatal surgery plays a role in surgical therapy, particularly in those patients who fail other forms of medical therapy. The specific role of palatal surgery, however, has been poorly understood until recently. Some patients achieve excellent results with significant symptomatic relief and a dramatic improvement in PSG measures, while others have had minimal improvement or even worsening of their apnea after traditional UPPP surgery.

Traditional UPPP was first described by Fujita in 1981, the same year that CPAP was introduced [52]. Although not as much was known at the time about the pathophysiology or cardiovascular sequelae of OSA, it represented a major treatment advance since, prior to 1981, tonsillectomy and tracheotomy were the only known effective surgical therapies. This ablative procedure essentially involves resection of tissue (mucosa, muscle, and glandular tissue) by removing the tonsils, uvula, and part of the soft palate.

Until recently, this particular procedure was largely unchanged and surgical series resulted in mediocre results at best, particularly when used as a sole procedure. In 1996, Sher et al. [2] attempted to summarize UPPP efficacy with a review of 37 papers and approximately 500 patients who underwent surgical therapy for OSA. These surgical series were hampered by poorly defined inclusion/selection criteria, variable surgical technique, and inconsistent follow-up. Sher defined surgical “success” as a postoperative respiratory disturbance index (RDI)  $<20$  with at least a 50% reduction from baseline, or an apnea index (AI)  $<10$  with at least a 50% reduction from baseline. Summarizing the data from these 500+ patients, a 41% “success” rate was reported. Although similar to long-term acceptable compliance rates with other forms of medical therapy, the overall results were unimpressive.

In many studies that followed, the subsequent goal was then to determine which patient factors predicted success and to preselect those patients for traditional UPPP who would fall into that 41%, rather than modifying and improving the surgery itself. This restricted approach, with essentially one treatment option, is problematic in that many patients are then left untreated if they are not deemed good candidates. Further, most patients have multilevel obstruction that requires more comprehensive

airway reconstruction rather than one isolated procedure. For the most part, the patients select the surgeon; the surgeon does not select the patients. Patients who fail other forms of medical therapy for sleep apnea present to the surgeon with hope to improve their symptoms, to improve their quality of life, and to improve their cardiovascular and general health. These patients seek additional treatment options, not simply to see if they are a candidate for one particular procedure.

## *A Paradigm Shift*

A major paradigm shift is underway with the fundamental goal of improved morbidity and effectiveness with more anatomically and physiologically sound reconstructive, rather than ablative, surgical procedures. As such, more recent advances have been directed toward properly phenotyping the airway and the specific anatomical pattern of obstruction, and therefore allowing customization of a surgical treatment algorithm for each patient, which often includes a palatal procedure.

Multiple prior studies of cases of UPPP failure have arrived at strikingly similar, and potentially shocking, conclusions. Whether using imaging, manometry, or videendoscopic techniques, approximately 84% of patients who have persistent disease after traditional UPPP have been shown to still have significant obstruction at the retropalatal portion of the airway [53]. In 1998, Langin aimed to evaluate the impact of UPPP on upper airway anatomy by posing the questions: (1) does traditional UPPP actually enlarge the oropharyngeal airway, and (2) could the outcome of UPPP be explained in terms of the morphological modifications produced by the surgery? Those patients who responded to palatal surgery with a successful reduction in the AHI (13 → 4) had a significant increase in the cross-sectional area at the level of the oropharynx. In contrast, the “non-responders” (AHI 14 → 25) had no change in the cross-sectional area, or in some cases even a smaller retropalatal airway, after palatal surgery [54].

These findings reinforce the idea that is not simply the level of obstruction that predicts surgical success; rather, it is the specific pattern of obstruction, proper selection of the specific type of palatal surgery, and proper execution of the surgical technique that determine results. In other words, just because a patient with palatal airway obstruction undergoes a palatal procedure does not mean that the palatal airway was adequately enlarged or stabilized.

Effectiveness is not the only factor driving the decision for surgery. Perioperative morbidity, side effects, and risk are just as important. Tracheotomy and bimaxillary advancement are quite effective but the associated morbidity precludes use in most patients. Serious perioperative complications of palatal surgery are uncommon (~1%) even in a large VA patient population with a high incidence of smoking [55]. Nevertheless, other side effects, such as globus sensation, mucous feeling, dry throat, and change in voice/swallowing, may be relatively common and underreported with traditional UPPP. These side effects can be quite bothersome to the patient and potentially irreversible.

## ***The Importance of Uvular Preservation***

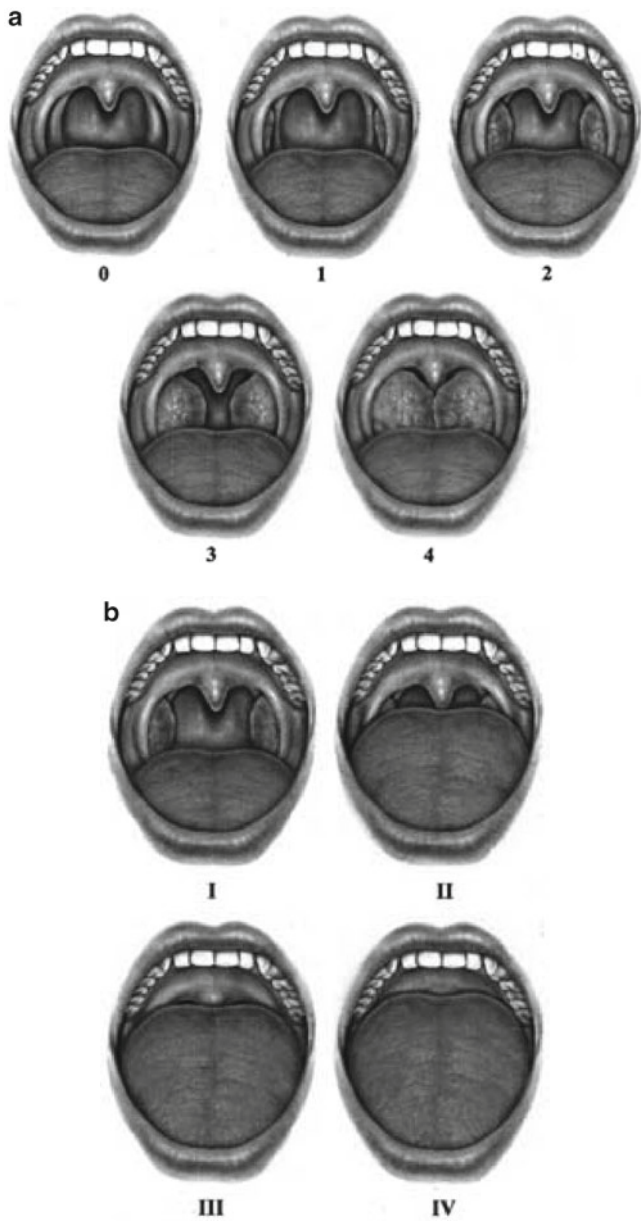
These benign, but often underreported, side effects may be significantly lessened by newer techniques and instrumentation designed to preserve mucosa, limit collateral thermal damage, and improve postoperative medical therapy. One of the most important changes, however, that may dramatically reduce morbidity and improve postoperative recovery and function is the preservation of the uvula. While traditional UPPP techniques involve resection of the entire structure of the uvula, current understanding of pharyngeal physiology suggests that the uvula is an important physiologic structure, rather than part of the airway problem in sleep apnea.

The uvular submucosa has a uniquely extensive immune cell population, primarily mast cells, that is important for the immunologic induction of mucosal tolerance to inhaled and ingested antigens [56]. The uvula has one of the highest concentrations of type II, fast-twitch, muscle fibers in the human body – essential for the quick coordinated movements of speech and swallowing function. Its glandular area also comprises highest concentration of serous glands (as opposed to mucous glands) in the oral cavity and oropharynx. The storage ducts are capable of quickly secreting, via muscle contraction, large volumes of serous fluid [57]. With videoendoscopic techniques, Back et al. [58] demonstrated that the uvula plays an essential role in basting the posterior pharyngeal wall with thin serous saliva. These findings likely explain the local pharyngeal side effects that occur in many patients undergoing traditional UPPP and in part serve as the basis for the development of newer, less morbid, and more effective palatal surgical procedures.

## ***Palatal Anatomy and Examination***

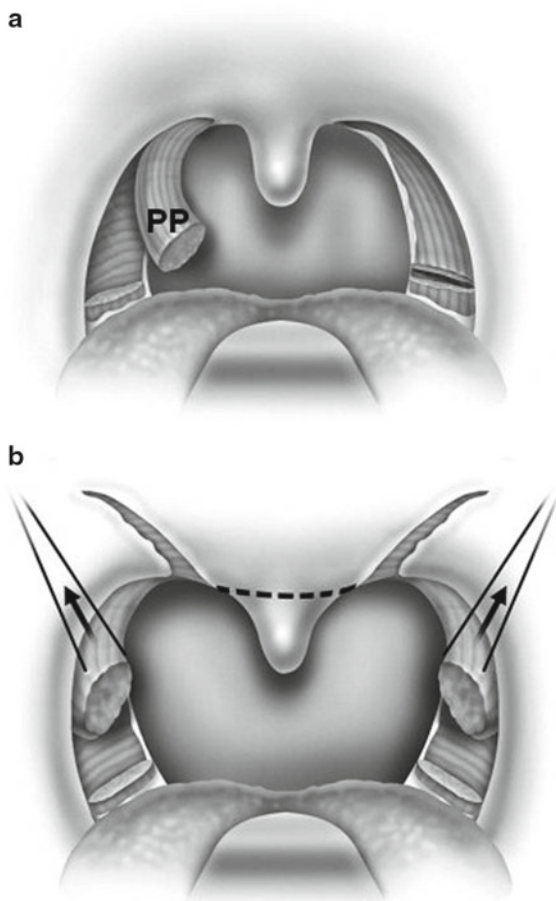
Proper procedure selection and execution are integrally dependent upon knowledge of the anatomy and physiology of the upper airway. Terms such as a “crowded airway” and even the Fujita classification are not sufficiently descriptive or useful in determining procedure selection and predicting success. The pharynx is best conceptualized anatomically as a muscle buttress system involving the palatopharyngeus and levator palatinus muscles, as well as the tensor palatini, palatoglossus, salpingopharyngeus, and uvular muscles. Physical examination of the oropharynx should include description of the palate/tongue relationship (Modified Mallampati or Friedman Tongue Position), tonsil size, lateral wall component (palatopharyngeus muscle), anterior/posterior depth, and vertical shape of the palate (Fig. 10.3).

Although many modifications and advances in palatal surgery have been reported, two procedures seem to be uniquely suited to improved effectiveness, via more anatomically sound technique, and reduced morbidity, via mucosal/uvula preservation: (1) expansion sphincter pharyngoplasty (ESP), and (2) transpalatal advancement pharyngoplasty. A more in-depth discussion of all available palatal procedures for OSA is beyond the scope and extent of this chapter. For further analysis of additional



**Fig. 10.3** Examination of the oropharynx: Examples of the methods used to stage and phenotype the oropharyngeal airway include (a) tonsil size, and (b) modified Mallampati or Friedman tongue/palate position. Reproduced from [72]

**Fig. 10.4** Expansion sphincter pharyngoplasty (ESP): Illustration of basic surgical principles of ESP. (a) After tonsillectomy, the palatopharyngeus muscle (PP) is isolated from the posterior tonsillar pillar, transected, rotated, and suspended submucosally. (b) The resultant effect is an anterior, superior, and lateral suspension (arrows) of the palatal insertion of the palatopharyngeus muscle and subsequent expansion of the lateral retropalatal ports with maximal mucosal preservation. The uvula can be shortened or contoured as needed but the uvular muscle and structure is generally left intact. Reproduced with permission from Elsevier Health Sciences [60]



palatal techniques, the reader is referred to Michael Friedman's surgical text, *Snoring and Obstructive Sleep Apnea* [59].

## ***Surgical Techniques***

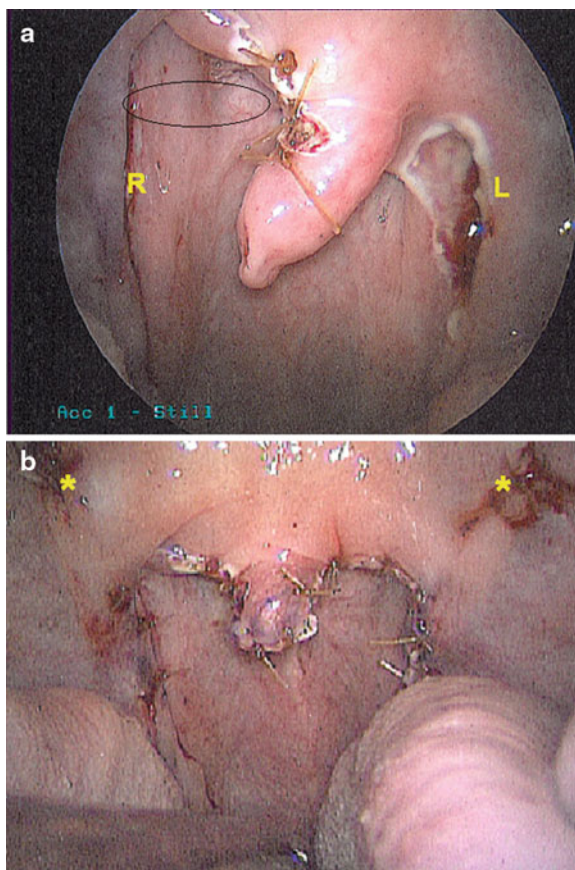
### **Expansion Sphincter Pharyngoplasty**

Many patients with retropalatal obstruction have a more obliquely oriented palate with a circumferential pattern of collapse and hypertrophied lateral pharyngeal walls. The anterior/posterior space between the hard palate and posterior pharyngeal wall is often open. Originally described by Woodson and Pang in 2007, ESP is uniquely suited to address this anatomy (Fig. 10.4).



**Fig. 10.5** ESP:

Intraoperative photographs of ESP. (a) The tonsils have been removed bilaterally with maximal mucosal preservation. ESP has been completed on the patient's right side (R) with a noticeable enlargement of the right retropalatal airway (*ellipse*), as compared to the unoperated left side (L). (b) Final intraoperative appearance after completion of ESP on both sides and contouring of the uvula. The anchor points of the palatopharyngeus suspension near the hamulus can be seen in the *upper right* and *left sides* of the photograph. Note the lateral expansion of the right retropalatal space with essentially no resection of tissue, minimal mucosal trauma, and preservation of the uvular structure



If present, the tonsils are first removed with maximal mucosal preservation. The palatopharyngeus muscles, which primarily account for the enlarged and medialized lateral pharyngeal walls, are isolated and suspended in an anterior, superior, and lateral vector towards the hamulus. The resultant effect is a dramatic opening of the retropalatal space in a lateral dimension, again with minimal to no resection of mucosa or other soft tissue. Additional contouring of the uvula and velum can be combined with the expansion pharyngoplasty; however, the bulk of the uvular structure and function is preserved (Fig. 10.5). The superior effectiveness of ESP, compared to traditional UPPP, has been established in a prospective randomized controlled trial (Table 10.5) [60].

### Transpalatal Advancement

Transpalatal advancement surgery is based on the concept that some patients have palatal anatomy that is more representative of maxillary deficiency/retrusion and



**Table 10.5** Results of a randomized controlled trial comparing AHI reduction with expansion sphincter pharyngoplasty (ESP) vs. traditional uvulopalatopharyngoplasty (UPPP)

	ESP	UPPP
Preoperative AHI	44.2	38.1
Postoperative AHI	12.0	19.6
<i>P</i> value	0.005	0.05
Mean change in AHI	32.3	18.5
Success rate <sup>a</sup> (%)	78.2	45.5

<sup>a</sup>AHI reduction >50% and AHI <15

Adapted with permission from Sage Publications [60]

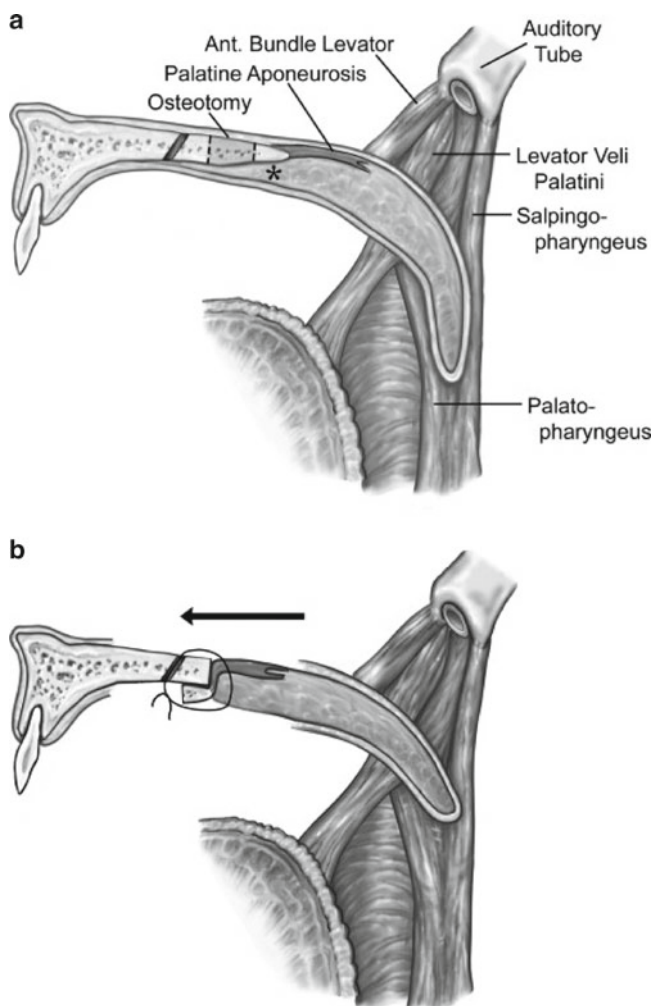
narrowing of the space between the posterior edge of the hard palate and the posterior pharyngeal wall. These patients generally have a more vertically oriented, low-lying, elongated soft palate, with a more anterior–posterior pattern of collapse (Fig. 10.6). Transpalatal advancement essentially involves an osteotomy that removes the posterior portion of the hard palate and advances the soft palate forward (Fig. 10.7). This procedure aims to achieve the enlargement of the retropalatal space similar to that obtained with a traditional maxillary advancement surgery, without the associated morbidity and potential cosmetic/dental changes.

Multiple studies have shown superior effectiveness compared to traditional UPPP with clinically significant improvement in the AHI (52 → 12), increase in the retropalatal airspace (+321%), and reduction in the critical closing pressure (−8.5 cm H<sub>2</sub>O) [61–63]. In a recent retrospective comparison between TPA and UPPP, after adjusting for other clinical factors, the odds ratio of surgical “success” was 5.8 with TPA compared to UPPP [64].

## Hypopharyngeal Surgery

### *Background*

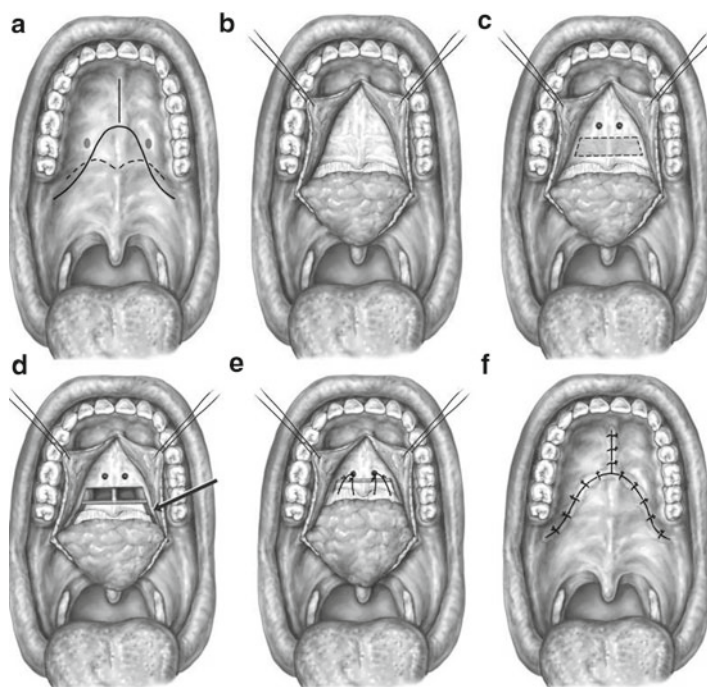
In the past, hypopharyngeal surgery was often relegated to patients with moderate–severe disease only or to those who first failed traditional UPPP. Technological advances have improved preoperative evaluation of the hypopharynx as well as intraoperative surgical exposure and postoperative recovery. Regardless of the sleep apnea severity, hypopharyngeal obstruction plays a role in most patients with OSA. Multilevel (nasal, oropharyngeal, and hypopharyngeal) obstruction is common in adult OSA patients, even in patients with mild disease [65]. In many patients who have failed medical therapy, surgical planning must include treatment of hypopharyngeal obstruction to improve treatment outcomes.



**Fig. 10.6** Transpalatal advancement: Mid-sagittal depiction of the concept of transpalatal advancement surgery for patients with maxillary deficiency and a more vertically oriented palate. A portion of the distal hard palate is removed (a) with subsequent advancement (b) of the soft palate and increased cross-sectional area of the retropalatal airspace. Reproduced with permission from Elsevier Health Sciences [73]

## Anatomy

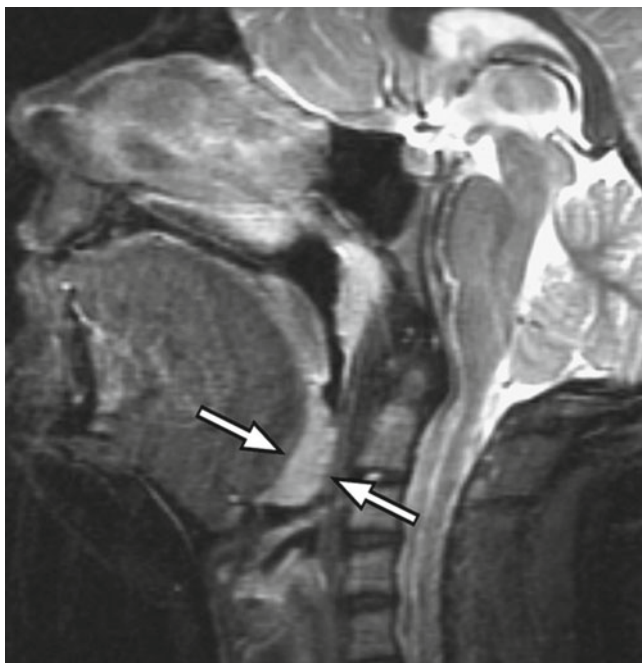
No single surgical procedure is warranted in all patients. Rather, just as in palatal surgery, proper procedure selection and execution must be dictated by each patient's anatomical pattern of obstruction. A variety of components can contribute to hypopharyngeal airway collapse including the lingual tonsils (Fig. 10.8), tongue base,



**Fig. 10.7** Transpalatal advancement: Diagram of the steps involved in transpalatal advancement surgery. (a) Depiction of the planned palatal incision (*solid lines*), junction of the hard and soft palate (*dashed line*), and location of the greater palatine foramina (*dots*). (b) Flap elevation and exposure of the hard palate. (c) Site of planned osteotomy (*dashed line*) and drill holes (*solid circles*). (d) After completion of the osteotomy and separation from the posterior nasal septum. (e) Sutures are placed through the drill hole anchors and around the posterior osteotomy and tensor aponeurosis, advancing the soft palate forward. (f) Closure of the incision and completion of the procedure. Note the preservation of the uvula and soft palate mucosa. Reproduced with permission from Elsevier Health Sciences [73]

epiglottis, and lateral pharyngeal walls. Evaluation of the specific pattern of collapse may be best achieved at this point in time with DISE as this provides direct visualization of the hypopharynx, in the supine position and in a dynamic state that mimics the lower genioglossus muscle tone of NREM sleep. Other options for the diagnostic assessment of hypopharyngeal obstruction include awake physical exam, supine awake nasolaryngoscopy, cephalometrics, and MRI.

The Moore classification (Fig. 10.9) of tongue base anatomy currently provides the best description of the anatomy and therefore assists in proper procedure selection [66]. A wide variety of both skeletal and soft-tissue reconstructive surgical procedures are available to address the hypopharynx, which in conjunction with the large variations in patients' anatomy, contributes to the difficulty in studying the effectiveness and obtaining clear data on these procedures. Many of the hypopharyngeal surgical techniques have been described in smaller case series and are confounded by the inclusion of other airway procedures.



**Fig. 10.8** Lingual tonsil hypertrophy: Sagittal magnetic resonance imaging (MRI) depicting hypertrophy (*arrows*) of the lingual tonsils and narrowing of the hypopharyngeal airway

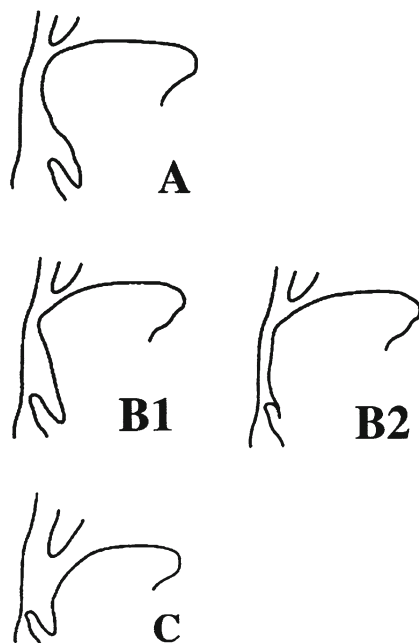
### *Hypopharyngeal Surgical Techniques*

Newer surgical techniques are rapidly evolving and resulting in improved effectiveness and much lower morbidity compared to past procedures. Volumetric reduction of the tongue base (midline glossectomy) with plasma technology appears to be a promising tool for effective enlargement of the hypopharyngeal airway, with relatively minimal discomfort, quick recovery to normal diet, and excellent results [67]. This technology now can be used to safely and effectively remove enlarged lingual tonsils as well, which in the past was often considered a procedure with difficult exposure and high morbidity [67].

Although radiofrequency reduction of the tongue base has been associated with subjective and objective sleep apnea improvement in a randomized clinical trial, histologic analysis suggests that the actual reduction in the tongue size is relatively small with radiofrequency reduction compared to more effective midline glossectomy techniques [68]. Nashi et al. [69] have demonstrated that significant fat deposition occurs in the tongue base as BMI increases. This finding again supports the need for procedures with substantial volumetric reduction and/or advancement of the tongue base as opposed to radiofrequency ablation alone.

One innovative solution on the horizon, that may address hypopharyngeal obstruction in through more physiologically sound mechanism, involves the stimulation

**Fig. 10.9** Moore tongue base classification: Sagittal depiction of different patterns of hypopharyngeal obstruction. *Type A*: high tongue base which predominantly reflects lingual tonsil hypertrophy. *Type B1*: high tongue base with retroepiglottic narrowing. *Type B2*: diffuse tongue base narrowing. *Type C*: primary retroepiglottic narrowing. Reproduced with permission from Elsevier Health Sciences [66]



**Table 10.6** Examples of minimally invasive surgical options for the specific treatment of hypopharyngeal obstruction

- Radiofrequency tongue base reduction
- Transoral submucosal endoscopic-assisted glossectomy
- Coblation lingual tonsillectomy
- Tongue base stabilization with suture suspension
- Genioglossus advancement
- Hyoid suspension

of the hypoglossal nerve through an implantable pacing device that coordinates with the patient's respiratory pattern [70]. Again, detailed discussion of the specific operative techniques and perioperative concerns is beyond the scope of this chapter and is available in Friedman's surgical text and atlas [59]. A sample list of hypopharyngeal surgical options is presented in Table 10.6.

## Maxillomandibular Advancement Surgery

Maxillomandibular advancement (MMA) commonly consists of a LeFort I maxillary osteotomy combined with sagittal split osteotomies of the mandible. The superior effectiveness of maxillomandibular skeletal advancement surgery has been fairly well established with rates of clinically significant improvement in subjective and objective OSA measures often exceeding 90% [71]. MMA succeeds because of

its sound anatomical principles, as referenced earlier in the oropharyngeal surgery section, of reconstructive (as opposed to excisional/ablational) enlargement of the airway on multiple levels. Nevertheless, the invasiveness, prolonged recovery, cosmetic changes, paresthesias, potential dental injury or malocclusion, and overall high morbidity preclude its use in most OSA patients, particularly those with mild to moderate disease.

The decision for surgery in any patient depends not only on effectiveness of the procedure but also on perioperative risk and morbidity. Tracheotomy is also an extremely effective surgical therapy for sleep apnea but is declined by the vast majority of patients because of the psychosocial implications and potential medical complications. MMA may be a reasonable treatment option for patients with severe persistent OSA despite prior medical and surgical failure or for patients with maxillomandibular deficiency or other craniofacial abnormalities; however, for the average OSA patient presented with this option, the morbidity and potential complications far outweigh the potential benefits.

## Conclusion

Numerous medical and surgical options exist for the treatment of sleep-disordered breathing. Although large numbers of patients are successfully managed with nasal CPAP, the most common form of medical therapy, many patients still fail to achieve adequate treatment over the long term and, clearly, there is a enormous demand for improved treatment options.

Surgical therapy does not play just one role in the management of OSA and does not consist of a sole treatment; rather, the goals of surgery depend on each patient's unique anatomy and clinical context. Surgery should be aimed at prevention of cardiovascular risk, symptom resolution, quality of life improvement, reduction of disease severity, or an adjunctive treatment to improve outcomes with other forms of medical therapy.

Successful surgical therapy is critically dependent on accurate diagnosis, skillful knowledge and examination of the upper airway anatomy, proper procedure selection, and proficient technical application. A major paradigm shift is underway to (1) properly phenotype each patient's multifactorial pattern of upper airway obstruction, and (2) customize a multilevel treatment plan with effective, low morbidity, reconstructive techniques, rather than the "sole site" excisional model commonly used over the past few decades.

## Summary of Keypoints

- Airway reconstructive surgery plays a key role in the management of many patients with OSA and has been demonstrated to successfully treat sleep-related symptoms as well as long-term disease morbidity.

- Evaluation of the effectiveness of surgical therapy is often complicated by the wide variety of procedures and different surgical techniques available, in addition to the ethical and practical concerns with instituting randomized controlled sham-procedure studies.
- Effective surgical therapy requires a systematic algorithm that addresses the entire upper airway, rather than one specific procedure or anatomical site. Successful management demands comprehensive knowledge of upper airway anatomy and physiology as well as the proper patient selection, procedure selection, and technique execution.
- In patients who fail medical therapy options or in some patients with particular anatomical features such as adenotonsillar hypertrophy, surgery may be employed as sole or primary therapy. The goals of sleep surgery, however, vary from patient to patient and can include reduction of cardiovascular risk, symptom resolution, quality of life improvement, reduction of disease severity.
- Surgical therapy also may be used as an adjunctive treatment to improve compliance and outcomes with other forms of medical therapy.
- Current state-of-the-art surgical therapy is characterized by (1) properly phenotyping each patient's unique anatomical pattern of upper airway obstruction, including the use of sleep endoscopy, and (2) customizing a multilevel treatment plan with effective, low-morbidity, reconstructive techniques, rather than the "sole site" excisional model commonly used over the past few decades.

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# Chapter 11

## Sleep and Lung Disease

Charles W. Atwood, Jr.

**Keywords** Hypoventilation • Neuromuscular disease • Obesity-hypoventilation syndrome • Chronic obstructive pulmonary disease • Kyphoscoliosis

### Introduction

Sleep disturbances are common in many respiratory disorders, including chronic obstructive pulmonary disease (COPD), asthma, and restrictive lung disease. Sleep is, in many ways, a time of vulnerability in respiratory illness. Changes in upper airway resistance and, at times, lower airway resistance, may exacerbate underlying pulmonary conditions. Sleep is also a time when hypoxemia may worsen, and this may impose its own associated health hazards. Since COPD and asthma are very common conditions, the burden of sleep-related physiological stress leads to a significant burden in terms of the number of people affected. Sleep in patients with less common lung diseases, such as restrictive disorders and obesity-hypoventilation syndrome, show different patterns of physiological abnormalities during sleep. In this chapter we will explore of the intersection between sleep and these important pulmonary medicine conditions.

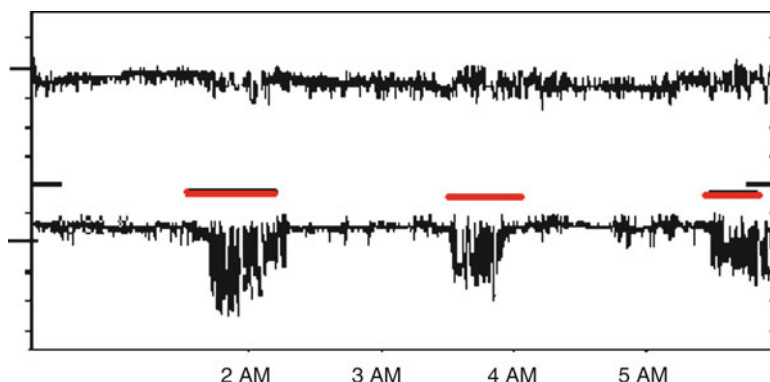
### Sleep and COPD

COPD is a common condition affecting approximately 14 million Americans [1]. COPD is commonly subdivided into chronic bronchitis and emphysema. Clinically, most patients have elements of each of these conditions in their day-to-day clinical

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**Fig. 11.1** An example of rapid eye movement (REM) sleep-related hypoventilation in a patient with chronic obstructive pulmonary disease (COPD). The *red horizontal bars* indicate the periods of desaturation. The *top signal* is heart rate. The *bottom signal* is oximetry. The *black horizontal bar* at the *Y* axis next to the heart rate indicates 90 bpm. The *horizontal bar* at the *Y* axis next to the oximetry channel indicates the 90% saturation mark. The patient experiences three periods of desaturation corresponding to the times he enters REM sleep

life with COPD. COPD experts tend to favor splitting chronic bronchitis and emphysema into relatively distinct syndromes, or phenotypes, as a way of understanding the pathophysiology of these two forms of chronic airflow obstruction. It is not clear whether this distinction is important at the individual patient level [2]. Treatment options tend to be similar regardless of the relative importance of the two forms of airflow obstruction in any one patient. Likewise, the differences between chronic bronchitis and emphysema do not seem crucial to understanding the interaction between sleep and airflow obstruction.

When the patient with COPD falls asleep, there is a rapid decrease in alveolar ventilation as the patient enters stages N1 and N2 sleep (the lighter stages of non-REM sleep). Depending on the severity of the lung disease, the patient may experience hypoxemia, which may exceed the magnitude of exercise-related hypoxemia. Sleep-associated hypoxemia in patients with COPD is due to a combination of sleep-induced hypoventilation and increased upper airway resistance [3].

## ***Hypoventilation***

Minute ventilation falls during all stages of sleep compared with wakefulness. This is a normal part of sleep physiology. Patients with significant lung disease, and who have gas transfer abnormalities at baseline, experience a greater degree of hypoxemia because of the combined effect of lung disease and hypoventilation. NREM sleep is associated with moderate hypoventilation, perhaps as much as a 20% decrease in alveolar ventilation from baseline levels wakefulness level. However, during rapid eye movement (REM) sleep, alveolar ventilation falls by as much as 40% [3] (Fig. 11.1). This is due to the skeletal muscle atonia, a physiological feature

unique to REM sleep. The diaphragm is among a few muscles that do not demonstrate active inhibition during REM sleep. However, accessory muscles of respiration are inhibited. Since many patients with advanced COPD use accessory muscles for ventilation, the loss in total ventilatory effort during REM sleep can be significant. Specifically, skeletal muscle atonia leads to a decrease in functional residual capacity with ensuing atelectasis, ventilation-perfusion mismatching, increased shuntfraction, and subsequent hypoxemia [4].

Phasic REM is the most vulnerable point in REM sleep for hypoventilation, as muscle paralysis extends even to the diaphragm. Transient episodes of diaphragmatic paralysis occur with phasic bursts of REMs [5]. Accordingly, hypoventilation in vulnerable patients is most pronounced, even on a routine polysomnogram, during phasic REM sleep.

Another contributor to hypoxemia during sleep in patients with COPD is increased upper airway resistance [6]. During non-REM sleep there may be an increased respiratory drive despite the fact that the overall degree of ventilation decreases. Increased respiratory drive is more than counterbalanced by upper airway resistance, which leads to the net effect of a decrease in ventilation by a moderate small to moderate amount.

The final mechanism contributing to COPD-related hypoxemia is the relative disadvantaged flat position of the diaphragm in advanced COPD. This may explain why nocturnal hypoxemia associated with COPD may be worse than the hypoxemia associated with other forms of chronic lung disease that do not affect the position of the diaphragm [7].

### ***Measurement of Hypoventilation and Respiratory Dysfunction***

It is difficult to assess individual mechanisms of hypoxemia during sleep, given the difficulty in assessing ventilation perfusion matching noninvasively [8]. A chief reason for the difficulty in making this measurement is the highly variable breathing rate and tidal volume during REM sleep. Likewise, lung perfusion is affected by the recumbent state during sleep where blood follows gravity and be directed to the posterior lungs. Ventilation tends to be more concentrated in the anterior lung. Depending on the location of emphysema in a given patient, the degree of increased lower airway resistance from airway involvement from COPD, and other factors, such as obesity, ventilation and perfusion relationships in COPD are variable, dynamic, and difficult to measure.

### ***Clinical Consequences of Sleep Hypoxemia in COPD***

Sleep hypoxemia in COPD may have several important effects on the health of the patient. There is compelling evidence that patients with COPD and hypoxemia have increased pulmonary artery pressures associated with the lowering of the  $\text{PaO}_2$

during sleep. This may lead to fixed pulmonary artery hypertension and may subsequent cor pulmonale [9]. One older study showed that the pulmonary arterial pressure rose from 37 to 55 mmHg during REM sleep while the average  $\text{PaO}_2$  fell to a low of 43 mmHg [10]. Animal models have shown that chronic hypoxemia for 2 h/day for 4 weeks can significantly increase right ventricular mass [11]. There are no parallel human data; however, it seems likely that chronic hypoxemia has a similar deleterious effect on the human myocardium.

Erythrocyte expansion is another consequence of chronic nocturnal hypoxemia. Nocturnal desaturation leads to increased erythropoiesis and expansion of the red cell mass. Morning erythropoietin levels are increased in some patients with COPD. Erythropoietin, however, does not appear to be stimulated until oxygen saturation falls to around 60% at night. It is likely there is a genetic predisposition to susceptibility to hypoxemia and increased erythropoiesis since not all COPD patients with similar degrees of nocturnal hypoxemia exhibit the same degree of erythropoiesis.

Poor sleep quality is a common complaint among patients with COPD. Sleep quality defined both subjectively (questionnaires) and objectively (variables on sleep studies) have been shown to be adversely affected. Arousals and sleep fragmentation are greater in hypoxemic COPD patients compared to those with normoxia [12]. However, poor sleep quality cannot be attributed solely to hypoxemia as patients with severe lung disease may have abnormal lung mechanics and report more dyspnea. Interestingly, excessive daytime sleepiness is not a frequent complaint, despite poor sleep quality.

The most serious acute complication of COPD with nocturnal hypoxemia is cardiac arrhythmias. The relationship between ventricular ectopy severity or frequency and nocturnal oxygen saturation is not very strong [13]. However, this may be a critical problem in patients with concomitant COPD and cardiac disease and may explain, at least partially, why heart disease is the leading cause of death in people with COPD.

### ***Diagnosis of Nocturnal Hypoxemia in COPD***

The diagnosis of nocturnal hypoxemia and COPD requires an overnight oximetry recording, which can be performed easily and inexpensively in the patient's home. For some patients it may be appropriate to request an overnight study in a specialized sleep laboratory. Polysomnography may be of value in such patients if obstructive sleep apnea (OSA) or another sleep disorder are suspected. For routine purposes, however, overnight oximetry is the appropriate first test.

### ***Treatment of Nocturnal Hypoxemia***

The primary treatment of nocturnal hypoxemia is supplemental oxygen [12, 14]. Nocturnal oxygen therapy is a straightforward therapeutic modality to prescribe. There is good evidence to support its use for improvement of quality of life [12, 14].

Guidelines that govern its use in the United States are available. The most commonly used set of guidelines are those of the Centers for Medicare and Medicaid Services (CMS). These guidelines state that if nocturnal hypoxemia is observed with oxygen saturation less than 88% for 5 min, supplemental oxygen may be prescribed. Supplemental oxygen may be prescribed if the oxygen saturation is 89% and there is clinical evidence of cor pulmonale, pulmonary hypertension, or erythrocythemia.

Despite having guidelines governing supplemental oxygen use, the evidence for providing oxygen therapy only during sleep is quite weak. There is extensive literature documenting benefits of oxygen to daytime hypoxemic COPD patients but this does not extend to prescribing oxygen for isolated nocturnal desaturation. Despite this lack of evidence, oxygen therapy for isolated nocturnal hypoxemia is commonly used. There are a number of unsettled questions about the treatment of nocturnal hypoxemia with supplemental oxygen. First, it is not known whether supplemental oxygen should be titrated during sleep or set at a fixed flow rate, with the expectation that any reduction in the burden of sleep-related hypoxemia would be beneficial. Titrating oxygen during sleep requires multiple nocturnal pulse oximetry tests, which would add cost to the patient's care.

Second, most practitioners do not routinely assess nocturnal hypoxemia in patients with COPD who are prescribed daytime oxygen. Rather, either they may continue the same liter flow during wakefulness during sleep or they may increase the liter flow by an arbitrary amount, such as 1 L/min, during sleep. One study demonstrated a reasonably linear relationship between daytime oxygenation and nocturnal oxygenation in patients with COPD [15], making it feasible to estimate if a patient would likely need nocturnal oxygen if their diurnal oxygen status were known. The authors concluded that measurement of nocturnal oxygenation did not add meaningful information to the assessment of daytime oxygen evaluation.

## ***Medications***

Several medications have been studied for their potential beneficial effect on reducing nocturnal hypoxemia. Almitrine is a respiratory stimulant that is available in Europe but not in the United States [16]; it may have a positive effect on ventilation and perfusion relationship. However, its side effects outweigh its putative clinical benefits. Older studies have examined the use of protriptyline, a tricyclic antidepressant with strong anticholinergic properties (and thus REM sleep suppressing properties) in the treatment of nocturnal hypoxemia with some showing benefit [17]. Protriptyline may improve nocturnal oxygenation by decreasing REM sleep and associated hypoventilation. However, it is not used, nor approved, for this indication, given its substantial side-effect profile. Finally, Medroxyprogesterone is a respiratory stimulant, which, theoretically, may decrease nocturnal hypoxemia. However, one double-blind placebo control trial showed no significant change in the nadir of oxygen saturation in a study of COPD patients who were taking the medication [18].

Alleviation of airflow obstruction is also expected to improve nocturnal oxygenation. Inhaled bronchodilators, such as beta agonists and anticholinergic bronchodilators may improve airway tone during sleep and one study has demonstrated improvements in sleep quality. Similarly, theophylline may improve nocturnal oxygen saturation through similar mechanisms. Nevertheless, beta agonists and theophylline may disrupt sleep.

In summary, there are no effective pharmacological agents that prevent or mitigate nocturnal hypoxemia in patients with COPD.

### ***Noninvasive Positive Pressure Ventilation***

Some patients may benefit from nocturnal intermittent positive pressure ventilation (NIPPV). This therapeutic technique was developed for patients with neuromuscular or chest wall disorders but has been extended to patients with severe COPD [19, 20]. The literature for this application is mixed, as many patients are unable to tolerate NIPPV. However, patients who tolerate NIPPV experience improvement in arterial blood gases and quality of life, and reduced healthcare expenditures.

### ***COPD and Obstructive Sleep Apnea: The Overlap Syndrome***

Both COPD and OSA are common conditions with a similar prevalence in the United States and most industrialized countries. Thus, some patients will have both conditions. The coincidence of OSA and COPD is called the “overlap syndrome” [21]. Patients with COPD should be asked about symptoms of OSA but routine testing for this condition without clinical suspicion is not recommended. Patients with the overlap syndrome may be at increase risk of more serious complications including cor pulmonale, chronic peripheral edema that may lead to venous stasis and severely impaired quality of life [21, 22]. Based on analyses from an ongoing large epidemiological study examining cardiopulmonary aspects of sleep apnea, COPD, and OSA do not have a common factor such that one modifies the other [23].

### ***Sleep and Asthma***

Asthma is a common disorder characterized by intermittent episodes of bronchoconstriction, dyspnea, wheezing, and chest tightness. The pathogenesis of asthma is airway narrowing due to edema and airway smooth muscle constriction. Airway caliber, inflammatory cell influx, and likely other related aspects of asthma pathogenesis have a well-defined circadian rhythm [24]. The sleep state is a major synchronizing factor for airway narrowing although sleep deprivation studies demonstrate airway narrowing despite the lack of sleep [24]. Mechanisms of airway



narrowing related to circadian timing or phase are not well understood but it is likely that factors such as the presence of specific allergens, airway cooling, alterations in mucus ciliary clearance and then pathological conditions, such as gastroesophageal reflux, may contribute to bronchial hyperreactivity. Sleep stages per se have not been shown to be significant factors in airway narrowing [25].

Other mechanisms which may influence asthmatic airway at night include autonomic function and circadian variation of certain hormones and catecholamines [26]. Cortisol contributes a modest amount to airway tone in normal individuals as well as asthmatics [27]. Circadian timing-related airway inflammation has been found in some but not all studies [28, 29]. The differences are likely due to inconsistencies in methodologies examining this question. Positive studies of airway inflammation focusing on circadian factors have found increases in inflammatory cells and bronchoalveolar lavage specimens at 4 a.m. compared to 4 p.m. [28, 30]. Similarly, pulmonary function tests such as FEV<sub>1</sub> show a nadir in the early morning hours compared to the afternoon hours. The mechanisms linking circadian rhythm biology and airway inflammation remain uncertain.

### ***Sleep Disturbances in Nocturnal Asthma***

Sleep disturbance is a common complaint of asthma patients who experience a worsening of their asthma at night. Nocturnal asthma symptoms may lead to worsening of daytime performance, including impaired daytime cognitive function, and the ability to perform at work and at school. Some patients may also develop nocturnal hypoxemia; however, the degree of oxygen desaturation is relatively mild [31–33].

### ***Diagnosis***

Then diagnosis of nocturnal asthma requires the appropriate combination of clinical symptoms such as nocturnal wheezing, cough, and shortness of breath associated with a greater than 10% fall in overnight peak flow rates. The treatment of nocturnal asthma is similar to the treatments offered to diurnal asthma control: inhaled bronchodilators, inhaled corticosteroids or oral corticosteroids, and leukotriene inhibitors. Some patients may require treatment with longer-acting beta agonist or a theophylline preparation in order to experience good control of nocturnal symptoms [34, 35].

### **Sleep and Restrictive Lung Disorders**

Restrictive lung disorders are those in which disorders of lung parenchyma, respiratory muscles, or the surrounding chest results in smaller than normal lung volumes. There is relatively little data regarding sleep in restrictive lung disorders caused by

parenchymal lung disease such as pulmonary fibrosis. In contrast, the neuromuscular and chest wall disorders have received more attention because of the recognition that noninvasive NIPPV results in significant physiological and clinical improvements for the patient suffering from these disorders.

### ***Chest Wall Disorders***

Chest wall disorders in which the chest is abnormally noncompliant can lead to respiratory failure. Severe obesity ( $\text{BMI} > 50 \text{ kg/m}^2$ ) and kyphoscoliosis are the two most common chest wall disorders. Post polio syndrome can lead to chest wall dysfunction but this is becoming less common with the United States' eradication of polio. Post polio syndrome can affect the chest wall with or without spinal curvature (scoliosis). Another vanishing cause of chest wall stiffening is "collapse" therapy for tuberculosis. This procedure led to both a stiffened chest wall that was made to collapse by resecting anterior ribs and allowing the anterior chest wall, no longer supported by ribs, to collapse on the lung. This caused a large degree of atelectatic lung and a restrictive pulmonary condition. This condition has now disappeared since we have been in the antibiotic era of tuberculosis therapy for the past 50 years.

Kyphoscoliosis refers to a combination of lateral as well as anterior–posterior curvature of the spine. Some patients may have pure scoliosis or appear kyphosis but most have a combination of the two. Chest wall deformity such as this is far more common in females than males. The prevalence of severe kyphoscoliosis is decreasing, owing to early intervention and corrective surgery before the development of respiratory complications. The current prevalence of kyphoscoliosis about 1:10,000 [36, 37].

### **Pathophysiology of Hypoxemia**

Respiratory mechanics in kyphoscoliosis demonstrate a significant restrictive defect [37], due to a stiffened chest and abnormally positioned respiratory muscles. Patients with kyphoscoliosis have smaller functional residual capacity and smaller oxygen stores in the lungs; thus, severe nocturnal hypoxemia is common. Patients with kyphoscoliosis may have rapid and severe desaturation during sleep and may tend to adopt a more rapid and shallow breathing pattern, which is probably advantageous from a muscle energy conservation standpoint but comes at the expense of ventilation; carbon dioxide rises [36]. Hypoxemia develops due to increasing ventilation–perfusion mismatch from increasing atelectasis from the changes in chest wall and diaphragm position. Increasing dyspnea and worsening hypoventilation lead to sleep fragmentation and poor sleep quality. In addition, patients with kyphoscoliosis are highly susceptible to respiratory failure if the respiratory drive is affected. This can be due to the inappropriate use of medications, for example, opiates

or sedative/hypnotics. Advanced kyphoscoliosis patients should be given oxygen judiciously since respiratory drive may be decreased by administration of supplemental oxygen above physiological levels [38].

## Diagnosis

The diagnosis of kyphoscoliosis is based on clinical and radiological assessment. Patients are at risk of ventilatory problems when the main curvature of the spine reaches an angle of at least 100°. Arterial blood gases should be measured to assess ventilation and oxygenation. If a PaCO<sub>2</sub> of 45 mmHg or higher is found then consideration should be given to nocturnal ventilation support [39]. In such patients sleep disruption, sleep fragmentation and, desaturations and elevated PaCO<sub>2</sub> contribute to sleep-related complaints, which are common as the condition advances.

## Therapy

The treatment goal is to improve ventilation, starting with NIPPV; however, some patients may require mechanical ventilation through a tracheostomy [39]. Kyphoscoliosis responds well to NIPPV, with improvement in sleep quality and quality. Although there are not randomized clinical trials comparing NIPPV with another therapy, the accumulated clinical experience has shown the value of this therapy.

## *Interstitial Lung Disease*

The Interstitial Lung Diseases are another group of disorders with restrictive physiology. This is a heterogeneous group of disorders, which affect lung parenchyma, resulting in scarring and stiffening of the lung and increases in its elastic recoil. The interstitial lung diseases do not result in significant hypoventilation until they reach end-stage. This is because the parental scarring and inflammation tends to stimulate hyperpnea, which has the effect of lowering PaCO<sub>2</sub> [40]. Sleep disruption, hypoxemia, and dyspnea may affect the quality in these patients. Cough may also be a debilitating symptom at night.

## Diagnosis

Sleep studies may be considered if there is a clinical suspicion of sleep apnea or other sleep disorders. It is particularly important to at least measure overnight oxygenation in patients demonstrating erythrocytosis since this may be a clinical clue to more severe levels of hypoxemia. Polysomnography has shown that interstitial lung disease patients have fragmented sleep, many arousals, more stage I sleep, and less REM sleep [41].

## Treatment

Interstitial lung disease patients may benefit from nocturnal oxygen therapy to treat underlying hypoxemia. However, noninvasive ventilation may be difficult, in light increased respiratory drive. Most of what we understand to be true about the effect of oxygen therapy on hypoxemia comes from studies of patients with severe obstructive airways disease [42]. Unfortunately, the literature on oxygen therapy in hypoxemic patients with interstitial lung disease is limited. Appropriate positive airway pressure or other treatments should be considered in patients who have concomitant OSA. Otherwise, oxygen therapy alone for patients with nocturnal hypoxemia alone will be sufficient.

## Sleep and Obesity: Hypoventilation Disorders

Obesity hypoventilation syndrome (OHS) consists of daytime and nocturnal hypoventilation after excluding other causes of alveolar hypoventilation, such as COPD, restrictive disorders, or neuromuscular diseases. The prevalence of OHS is unknown. As its name suggests, this condition afflicts obese individuals. Yet, only a minority of obese patients will have obesity hypoventilation (10–20%) [39]. This degree of obesity may be more common in women than in men but more men appeared to be diagnosed with OHS.

The major risk factor is obesity. There may be other factors relating to control of breathing which predispose one to developing obesity hypoventilation, but these mechanisms remained poorly understood and are not easily clinically identifiable.

## Pathogenesis

Abnormalities in respiratory mechanics, control of breathing and state changes related to sleep vs. wakefulness seem to be the most important factors in development of OHS [38, 39, 43]. Abnormalities in lung mechanics are more pronounced in patients with OHS compared to patients with eucapnic morbid obesity [43]. Reduced ventilatory drive may also contribute to the development of OHS. Patients with OHS have a blunted ventilatory drive compared to obese individuals without OHS. Whether the defect in ventilator drive is acquired or familial is unclear [44–46].

Several biochemical factors may influence the development of OHS, including leptin and serum bicarbonate levels. Leptin is an adipose tissue-derived hormone with many different effects, including serving as a respiratory stimulant. In one animal model, the leptin-deficient *ob/ob* mouse, exogenous administered to the mice caused a reversal in OHS [47]. Obesity hypoventilation and OSA are leptin-resistant states. This fits the empiric evidence that leptin levels are high, not low, in OHS and OSA. The concept of central leptin resistance has been proposed to explain

high leptin levels in OHS patients who also seem to have blunted respiratory responses [48, 49]. Metabolic compensation for chronic respiratory acidosis is associated with accumulation of bicarbonate and blunted chemoresponsiveness. This tends to promote daytime hypercapnia [38].

### *Clinical Features*

In addition to symptoms associated with morbid obesity, OHS patients may present with peripheral edema, venous stasis, pulmonary hypertension, and cor pulmonale. Dyspnea on exertion is common [38, 39]. OHS patients consume a higher amount of health services compared to very obese but eucapnic patients [50]. Obesity hypoventilation patients exhibit greater degree of cardio metabolic complications than patients who have OSA or severe eucapnic obesity alone.

### *Diagnosis*

The diagnosis of OHS consists of an elevated  $\text{PaCO}_2$  in an awake patient. The symptoms of OHS are not adequately specific to be use in making a diagnosis. The diagnosis often requires a high index of suspicion. Elevated serum bicarbonate is a useful laboratory clue to the possibility of  $\text{CO}_2$  retention. A serum bicarbonate level  $\geq 27$  mEq/L is highly sensitive (92%) but not specific (50%) for the presence of an elevated  $\text{CO}_2$  level. Pulse oximetry is not helpful in diagnosing OHS. Transcutaneous  $\text{CO}_2$  measurements may be very helpful in documenting elevation in  $\text{CO}_2$  and strongly suggesting the disorder is present [39].

### *Therapy*

The treatment of choice for OHS is positive pressure therapy, either CPAP or bilevel positive airway pressure (BPAP). Both modalities will improve alveolar ventilation. However, BPAP is capable of providing greater ventilator support than CPAP. If the difference between the inspiratory positive airway pressure (IPAP) and the expiratory positive airway pressure (EPAP) is at least 6, then ventilation is likely to be effective. Longer-term studies have suggested that positive airway pressure therapy remains effective for OHS patients and result in improved arterial blood gas values, daytime sleepiness, and ventilatory responsiveness to carbon dioxide re-breathing [51]. Studies have also demonstrated decreased health care utilization of decreased hospitalizations than the patients with OHS treated with positive airway pressure therapy [50]. In addition to positive airway pressure therapy, some patients may benefit from low flow oxygen either alone or with BPAP to maintain adequate oxygen saturation.

Surgery may be a useful adjunct to positive airway pressure therapy for obesity hypoventilation. Upper airway surgery, which is sometimes effective for OSA, does not have a significant role in OHS. Tracheostomy, however, may be effective treatment. Nocturnal ventilation through a tracheostomy is an effective method of increasing alveolar ventilation. Monitoring arterial blood gases periodically is essential for monitoring the effectiveness of the therapy [39].

## ***Weight Loss***

Weight loss is an effective treatment for OHS. However, it is difficult to achieve and maintain long-term. Bariatric surgery, with the goal of achieving and sustaining significant weight loss, is an option for obese patients with significant hypoventilation. Bariatric surgery is increasingly accepted as a definitive treatment for severe obesity. The degree of weight loss that is possible with bariatric surgery has been shown to improve gas exchange and lung volumes, especially the expiratory reserve volume [52]. Unfortunately, we have few long-term data in patients with well-described OHS who have undergone bariatric surgery and then continued in follow-up to establish response of OHS to significant weight loss. However, if we extrapolate from the experience with OSA, then we can expect significant improvement in pulmonary physiological parameters and OHS symptoms, although there will be many patients who are not fully cured of the OHS [53].

## **Summary of Keypoints**

- Sleep disturbances are common in chronic respiratory conditions. These include poor sleep quality and worsening gas exchange.
- REM sleep is characterized by significant alveolar hypoventilation, due to skeletal muscle atonia, reduced during volume, and subsequent worsening of ventilation/perfusion mismatching.
- Nocturnal hypoxemia is due to a combination of hypoventilation ventilation/perfusion mismatching.
- Nocturnal oximetry is sufficient for the diagnosis of nocturnal hypoxemia. Polysomnography should be reserved for situations where a specific sleep disorder, such as OSA is suspected.
- Noninvasive ventilation may be beneficial in patients with COPD and chronic ventilatory failure, chest wall disease, or obesity hypoventilation.
- Clinicians should specifically inquire about sleep in patients with chronic lung disease, including poor nocturnal sleep, insomnia, morning headache, and daytime hypersomnia.

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# Chapter 12

## Central Sleep Apnea

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**Keywords** Central apnea • Hypoventilation • Hyperventilation • Hypocapnia • Cheyne–Stokes respiration • CPAP • Adaptive servo-ventilation

Central sleep apnea is a manifestation of breathing instability in a variety of clinical conditions and is often bundled under the rubric of obstructive sleep apnea. Central sleep apnea occurs because of a transient cessation of ventilatory motor output, under several physiologic or pathologic conditions. This chapter will address the pathogenesis, clinical features, and management of central sleep apnea.

### Determinants of Central Apnea During NREM Sleep

#### *Hypocapnia*

The sleep state (specifically non-rapid eye movement or NREM sleep) removes the wakefulness “drive to breathe” and renders respiration critically dependent on chemical influences, especially  $\text{PCO}_2$ . Central apnea results if arterial  $\text{PCO}_2$  is lowered below a highly sensitive “apneic threshold” [1, 2]. Hypocapnia is a potent but not an omnipotent mechanism of reduced ventilatory motor output during NREM sleep. Several factors modulate and mitigate the effects of hypocapnia on ventilatory motor output and promote stability of respiration

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### Short-Term Potentiation

Actively induced hyperventilation (such as hypoxic hyperventilation) is associated with activation of an excitatory neural mechanism referred to as short-term potentiation (STP) [3–5], which results in a gradually return of ventilation toward the baseline upon cessation of the stimulus to breathe. STP has been demonstrated in humans as well as in animals and is unaffected by the state of consciousness. STP may play a significant role in preserving rhythmic respiration by preventing abrupt drop in ventilation during transient hypocapnia such as following brief hypoxia or transient arousal. In fact, central apnea rarely occurs following termination of brief hypoxia, despite hypocapnia at or below the apneic threshold [3, 5]. Similarly, although hypocapnia occurs during transient arousals from sleep, the activation of STP may mitigate the occurrence of central apnea under these conditions [6]. However, prolonged hypoxia may abolish STP by, which may explain the development of periodic breathing after 20–25 min of hypoxia and the occurrence of central apnea upon termination of prolonged hypoxic exposure [5, 7].

### Duration of Hyperpnea

The duration of hyperpnea is another important determinant of reduced ventilatory motor output following hyperventilation. Central apnea does not usually occur following brief in sleeping humans [8] or dogs [9] possibly due to insufficient reduction in  $\text{PCO}_2$  at the level of the central chemoreceptors.

In summary, the balance between hypocapnia and short-term potentiation determines the occurrence of post-hyperventilation apnea during stable sleep, while the duration of hyperventilation may determine whether the reduction in medullary  $\text{PCO}_2$  is sufficient for the development of central apnea.

### Role of Upper Airway Reflexes

While hypocapnia is the most common influence leading to central apnea, other mechanisms may also induce central apnea. For example, negative pressure-induced deformation of the isolated upper airway causes central apnea in dogs during both wakefulness and sleep [10]. Whether such reflexes contribute to the developments of central apnea in sleeping humans remains speculative. Conversely, central apnea occurs more frequently in the supine position [11–13] and may be reversed with nasal continuous positive airway pressure (CPAP) [14]. Likewise, there is evidence of supine dependency including that the lateral position amelioration of severity of central apnea and Cheyne–Stokes respiration [11–13].

## Mechanisms Perpetuating Breathing Instability

Central apnea does not occur as a single event, but as cycles of apnea/hypopnea alternating with hyperpnea. Ventilatory control during sleep operates as a negative-feedback closed-loop cycle to maintain homeostasis of blood gas tensions within a physiologic range. Many authors have adopted the engineering concept of “loop gain” as a measure of ventilatory stability or susceptibility to central apnea and recurrent periodic breathing [15]. Loop gain represents the overall response of the plant (representing the lung and respiratory muscles), the controller (representing the ventilatory control centers and the chemoreceptors) and the delay, dilution and diffusion inherent in transferring the signal between the plant and the controller. A detailed discussion of the dynamics of ventilatory control is beyond the scope of this chapter there are several excellent reviews that have discussed this aspect in detail [16–18].

The occurrence of central apnea is associated with several consequences that conspire to promote further breathing instability:

- Once ventilatory motor output ceases, rhythmic breathing does not resume at eupneic arterial  $\text{PCO}_2$  ( $\text{PaCO}_2$ ) due to inertia of the ventilatory control system; an increase in  $\text{PaCO}_2$  by 4–6 mmHg above eupnea is required for resumption of respiratory effort [19].
- Central apnea is associated with narrowing or occlusion of the pharyngeal airway [20]. Thus, resumption of ventilation requires opening of a narrowed or occluded airway and overcoming tissue adhesion forces [21] and cranio-facial gravitational forces.

Termination of central apnea is associated with variable changes in arterial blood gases (hypoxia and hypercapnia) and transient EEG arousal, resulting in ventilatory overshoot, subsequent hypocapnia, and a recurrence of apnea/hypopnea. This sequence explains why apnea rarely occurs as a single event (i.e., “apnea begets apnea”) and why there is an overlap between central and obstructive apnea (upper airway obstruction often follows central apneas upon resumption of respiratory effort, i.e., mixed apnea).

## Pathophysiologic Classification of Central Sleep Apnea

Central apnea syndrome may be present in a diverse group of conditions including heart failure and obstructive sleep apnea. The ICSD lists several categories of central apnea: (1) Primary Central Sleep Apnea, (2) Central Sleep Apnea Due to Cheyne–Stokes Breathing Pattern, (3) Central Sleep Apnea Due to Medical Condition Not Cheyne–Stokes, (4) Central Sleep Apnea due to High Altitude Periodic Breathing, (5) Central Sleep Apnea Due to Drug or Substance use. Central apneas are caused either by hyperventilation or hypoventilation.

Primary CSA, CSA-CSR, and CSA at high altitude are examples of CSA-related to hyperventilation. Central Sleep Apnea Due to Drug or Substance use is due to hypoventilation, whereas central apnea associated with other medical conditions may be due to either hyperventilation or hypoventilation. The underlying mechanisms influence the choice of therapy including optimization of medical therapy in central apnea associated with other conditions such as heart failure, hypothyroidism, or acromegaly.

The level of arterial  $\text{PCO}_2$  during wakefulness is often used to classify central apnea as hypercapnic or non-hypercapnic. However, such classification does not capture the underlying pathogenesis as apnea represents hypoventilation or a consequence of hyperventilation.

### ***Central Sleep Apnea Secondary to Hypoventilation***

The sleep state is associated with reduced ventilatory motor output, increased upper airway resistance and hypoventilation. This physiologic constellation carries pathologic consequences in patients with an underlying abnormality in ventilatory control or impaired pulmonary mechanics. Most afflicted patients suffer from a central nervous system disease (e.g., encephalitis), neuromuscular disease (e.g., post-polio syndrome), or severe abnormalities in pulmonary mechanics (e.g., kyphoscoliosis [22]). *Thus, the hallmark of this disease is alveolar hypoventilation representing nocturnal ventilatory failure or worsening of the underlying chronic disease.* Arousal from sleep restores alveolar ventilation to a variable degree; resumption of sleep reduces ventilation in a cyclical fashion.

Central apnea secondary to hypoventilation does not necessarily meet the strict definition of “apnea,” since feeble ventilatory motor output may persist albeit below the thresholds required to preserve alveolar ventilation. Likewise, it may not meet the definition of “central” in patients with respiratory muscle disease or skeletal deformities. Consequently, the presenting clinical picture includes both features of the underlying ventilatory insufficiency (e.g., morning headache, cor pulmonale, peripheral edema, polycythemia, and abnormal pulmonary function tests) and features of the sleep apnea/hypopnea syndrome (e.g., poor nocturnal sleep, snoring, and daytime sleepiness).

A rare but interesting group of patients present with primary alveolar hypoventilation manifesting by daytime hypoventilation without an apparent identifiable cause and blunted chemo responsiveness [23, 24]. Congenital central hypoventilation syndrome (CCHS) results from a mutation in the gene that encodes the homeobox (PHOX) 2B gene.

The mechanism(s) responsible for hypercapnic central sleep apnea in a given patient influence(s) the management strategy, which aims to restore effective alveolar ventilation during sleep. Treatment of choice is assisted ventilation; Nasal CPAP and supplemental oxygen are unlikely to alleviate the condition.

## ***Central Apnea Secondary to Hyperventilation***

Hypocapnia secondary to hyperventilation is the most common underlying mechanism of central apnea. A typical patient with non-hypercapnic central apnea has no evidence of a neuromuscular disorder, abnormal lung mechanics, or impaired responses to chemical stimuli. Accordingly, apnea is a result of a transient instability rather than a ventilatory control defect.

How does the first apnea begin? Several transient perturbations may trigger the initial event, including oscillation in sleep state [25], or transient hypoxia possibly due to retention of secretions or reduced lung volumes at sleep onset. Thus, hypoxia stimulates ventilation, subsequently leading to hypocapnia and apnea. The occurrence of apnea initiates the repetitive process of apnea-hyperpnea and leads to sustained breathing instability, manifested as periodic breathing (see above). In summary, non-hypercapnic central apnea is a heterogeneous entity that may be an idiopathic or a secondary condition. The pathogenesis may vary depending upon the clinical condition. However, hypocapnia secondary to hyperventilation is the common denominator in this group of disorders.

## **Central Apnea Risk Factors**

### ***Sleep State***

Transient breathing instability and central apnea often occur during the transition from wakefulness to NREM sleep. As sleep state oscillates between wakefulness and light sleep [26–28] the level of  $\text{PaCO}_2$  is at or below the hypocapnic level required to maintain rhythmic breathing during sleep (i.e., the “apneic threshold”), resulting in central apnea; recovery from apnea is associated with transient wakefulness and hyperventilation. The subsequent hypocapnia elicits apnea upon resumption of sleep. Consolidation of sleep alleviates the oscillation in sleep and respiration and stabilizes  $\text{PaCO}_2$  at a higher set point above the apneic threshold. Interestingly, central apnea may occur without preceding hyperventilation at the transition from alpha to theta in normal subjects is associated with prolongation of breath duration [29]. Although most authors believe that central apnea at sleep onset may be a normal phenomenon; the natural history of this “phenomenon” is unknown.

Central sleep apnea is uncommon during REM sleep as many studies suggest that breathing during REM sleep is impervious to chemical influences (REF), possibly due to increased ventilatory motor output during REM sleep [30, 31] relative to NREM sleep. In addition, there is evidence in animal studies that hypocapnia, per se, may decrease the amount of REM sleep [32]. The major barrier to answering this question in humans is the difficulty in conducting such experiments without disrupting REM sleep.

The loss of intercostal and accessory muscle activity during REM sleep leads to a reduction of alveolar ventilation. This may manifest as apparent central apnea or hypopnea in patients with compromised lung mechanics or neuromuscular disease. If severe diaphragm dysfunction is present, nadir tidal volume may be negligible and the event may appear as central apnea. Thus, central apnea during REM sleep represents transient hypoventilation rather than post-hyperventilation hypocapnia.

## *Age and Gender*

Central sleep apnea is more prevalent in older adults relative to middle-aged individuals [33–35] physiologically; sleep state oscillations may precipitate central apnea in older adults [36]. Increased prevalence of co-morbid conditions such as thyroid disease [37], congestive heart failure [38], atrial fibrillation [39], and cerebrovascular disease [40], may also contribute to increased susceptibility to develop central apnea in older adults.

Central sleep apnea is uncommon in pre-menopausal women [41]. There is evidence that women are less susceptible to the development of hypocapnic central apnea during relative to men following mechanical ventilation. Physiologically, the hypocapnic apneic threshold is higher in men relative to women. Using nasal mechanical ventilation during stable NREM sleep, Zhou et al. [2] have shown that the apneic threshold was  $-3.5$  vs.  $-4.7$  mmHg below room air level in men and women respectively. This difference was not due to progesterone. In fact, administration of testosterone to healthy pre-menopausal women for 12 days resulted in an elevation of the apneic threshold and a diminution in the magnitude of hypocapnic required for induction of central apnea during NREM sleep [42]. Conversely, suppression of testosterone with leuprolide acetate in healthy males decreases the hypocapnic apneic threshold and potentially stabilizing respiration [43]. Thus, male sex hormones are the most likely factor elevating the apneic threshold in men.

## *Medical Conditions*

Sleep apnea is highly prevalent in patients with CHF [38, 44–46]. Javaheri et al. [45] demonstrated that 51% of male patients with CHF had sleep-disordered breathing; 40% had central sleep apnea, and 11% obstructive apnea. Risk factors for CSA in this group of patients include male gender, atrial fibrillation, age  $>60$  year, and daytime hypocapnia ( $PCO_2 < 38$  mmHg during) [47]. Risk factors for OSA differed by gender; the only independent determinant in men was Body mass index (BMI), whereas age over 60 was the only independent determinant in women.

Hyperventilation is a common breathing pattern in patients with CHF, who demonstrate daytime hypocapnia and minimal or no rise in  $P_{ET} CO_2$  from wakefulness to sleep [48]. Chronic hyperventilation results in decreased plant gain [49, 50], which

mitigates the magnitude of hypocapnia for a given increase in alveolar ventilation. In other words, steady-state hyperventilation and hypocapnia are potentially stabilizing rather than destabilizing as is commonly thought. Increased propensity to central apnea in patients with CHF is due to increased hypocapnic chemosensitivity (increased controller gain).

Sleep apnea is also common after a cerebrovascular accident (CVA) [40]; with central apnea being the predominant type in 40% of patients of sleep apnea after a CVA [51, 52]. Likewise, central apnea occurs in 30% of patients who are on stable methadone maintenance treatment [53]. Finally, several medical conditions predispose to the development of central apnea including hypothyroidism, acromegaly, and renal failure have an unexpectedly high prevalence of sleep apnea [54–56]. Nocturnal hemodialysis is associated with improvement in sleep apnea indices [56].

Some patients with central apnea have no apparent risk factor and are deemed to have “idiopathic central apnea”; typically, these patients demonstrate increased chemoresponsiveness and sleep state instability [57]. It is plausible that these patients will have occult cardiac or metabolic disease. For example, idiopathic central sleep apnea is more prevalent in patients with atrial fibrillation [39].

## Clinical Features and Diagnosis

The clinical presentation includes features of the underlying disease and features of sleep apnea syndrome. Patients with central apnea secondary to hyperventilation may present with the usual symptoms of sleep apnea syndrome. Alternatively, they may present with *insomnia* and *poor nocturnal* addition. Frequent oscillation between wakefulness and stage 1 NREM sleep may promote *sleep fragmentation* and *poor nocturnal sleep* as the presenting symptoms.

Central sleep apnea may also be found as an incidental polysomnographic finding in a patient with obstructive sleep apnea, either on the initial diagnostic study or after restoring upper airway patency with nasal CPAP. The latter is referred to as “complex sleep apnea,” implying a distinct clinical entity. However, it is likely that this phenomenon represents unmasking of the underlying breathing instability in patients with obstructive sleep apnea and may resolve spontaneously [58, 59].

Nocturnal polysomnography is the standard diagnostic method including measurement of sleep and respiration, including detection of flow, measurement of oxyhemoglobin saturation, and detection of respiratory effort. Detection of respiratory effort is important to distinguish central from obstructive apnea. Most clinical sleep laboratories utilize surface recording of effort to detect displacement of the abdominal and thoracic compartments instead of esophageal pressure recording.

The presence of cardiogenic oscillations (pulse artifacts) on the flow signal has been used as an indirect index of central etiology. The underlying rationale is the pulse artifacts represent transmission of a pulse waveform from the thorax, and hence indicates a patent upper airway that allows the transmission of cardiogenic oscillation.



Morrell et al. [60] used fiber optic naso-pharyngoscopy to evaluate upper airway patency during central apnea; cardiogenic oscillations were present even when the airway is completely occluded. Thus, the presence of cardiogenic oscillations does not prove upper airway patency or central etiology.

## Management

Central apnea syndrome is a disorder with protean manifestations and underlying conditions. The presence of co-morbid conditions and concomitant obstructive sleep apnea influence therapeutic approach significantly. Specific therapeutic options include positive pressure therapy, pharmacologic therapy, and supplemental oxygen.

### *Positive Pressure Therapy*

Central apnea may respond to nasal CPAP therapy, especially if in combination with episodes of obstructive or mixed apnea. If a concomitant clinical condition is present, such as congestive heart failure, hypothyroidism, or acromegaly, optimization of medical therapy is also required and may ameliorate the severity of central apnea. Likewise, central sleep apnea in patients with obstructive sleep apnea may resolve with alleviation of upper airway obstruction with positive pressure therapy. Many patients with idiopathic central sleep apnea receive a trial of nasal CPAP, which has been shown to reverse central sleep apnea, even in the absence of obstructive respiratory events [14], especially supine-dependent central sleep apnea. The response may be due to preventing upper airway occlusion during central apnea and subsequent ventilatory overshoot [20]. Prevention of ventilatory overshoot may explain the reported combination of reduced apnea frequency and increased PCO<sub>2</sub> after CPAP [61]. Nasal CPAP is the initial option during a therapeutic titration study, despite the lack of systematic studies on nasal CPAP therapy in patients with idiopathic central apnea.

The exuberance regarding nasal CPAP therapy in patients with central apnea and CHF did not withstand the rigors of controlled clinical trials. The Canadian Continuous Positive Airway Pressure trial, or Can PAP [62] tested the hypothesis that CPAP would improve the survival rate without heart transplantation in patients with heart failure and central sleep apnea. The study enrolled 258 patients who had heart failure and central sleep apnea; participants were randomly assigned to the nasal CPAP treatment group ( $n=128$ ) or no CPAP (130 patients). Duration of follow-up was for a mean of 2 years. There was greater improvement in the CPAP group at 3 months relative to the placebo group as evidenced by greater reductions in apnea-hypopnea index, ejection fraction, mean nocturnal oxyhemoglobin saturation, plasma nor-epinephrine levels, and the distance walked in 6 min at 3 months. Nevertheless, there was no difference in the overall event rates (death and heart transplantation) between the two groups. Thus, nasal CPAP had no effect on

survival, despite the effect on the “severity” of central apnea and several intermediate outcome variables. Therefore, current evidence does not support the use of CPAP to extend life in patients who have heart failure and central sleep apnea.

Non-invasive positive pressure ventilation (NIPPV) using pressure support mode (bi-level nasal positive pressure) is effective in restoring alveolar ventilation during sleep. Clinical indications include nocturnal ventilatory failure and central apnea secondary to hypoventilation. There is evidence that NIPPV exerts a salutary effect on survival in patients with ventilatory failure secondary to amyotrophic lateral sclerosis [63]. It is unclear whether NIPPV exerts a similar effect in other neuromuscular conditions associated with nocturnal ventilatory failure. However, the overall evidence supports the use of NIPPV in a pressure support mode to treat central sleep apnea secondary to hypoventilation, such as neuromuscular or chest wall-related nocturnal hypoventilation. If the ventilatory motor output is insufficient to “trigger” the mechanical inspiration, adding a backup rate ensure adequate ventilation.

Treatment of central apnea secondary to hyperventilation using nasal pressure support ventilation in the bi-level mode may result in worsening of central apnea and breathing instability owing to augmented ventilatory overshoot and hypocapnia [64]. The work of Meza et al. [65] provides empiric evidence that pressure-support ventilation results in periodic breathing and recurrent central apnea when the pressure gradient is above 7 cm H<sub>2</sub>O. The addition of a backup rate would be required to maintain stable respiration, which would convert ventilatory support to controlled mechanical ventilation. In general, Bi-level positive pressure therapy is unlikely to alleviate central apnea, without a back up rate. Nevertheless, Bi-level PAP may ameliorate central apnea that accompanies severe obstructive apnea by preventing upper airway obstruction and ventilatory overshoot.

Recent technological advances allowed for variations in the mode of delivering positive pressure ventilation. One example is Adaptive Servo-Ventilation (ASV), which provides a small but varying amount of ventilatory support and a back up rate, against a background of low level of CPAP. The device maintains ventilation at 90% of a running 3-min reference period; thus, changes in respiratory effort results in reciprocal changes in the magnitude of ventilatory support. There is evidence that ASV is more effective than CPAP, Bi-level pressure support ventilation, or increased dead space in alleviating central sleep apnea [66]. However, there are no long-term studies examining the long-term effectiveness or outcome. Therefore, the decision to initiate ASV hinges on the efficacy of the treatment in normalizing AHI, patient preference, payers preference, and the availability of the requisite support for adherence or troubleshooting.

## ***Pharmacological Therapy***

Pharmacologic therapy for central apnea remains elusive, and there are no controlled clinical trials demarcating the boundaries of effectiveness [67]. Several small clinical trials indicate that acetazolamide or and theophylline may be beneficial in the treatment of central apnea [68, 69]. Acetazolamide is a weak diuretic and a carbonic

anhydrase inhibitor that causes mild metabolic acidosis. Acetazolamide ameliorates central sleep apnea when administered as a single dose of 250 mg before bedtime [68]. Likewise, theophylline ameliorates the severity of Cheyne–Stokes respiration in patients with CHF [69], without adverse effect on sleep architecture. Pharmacologic therapy remains an unfulfilled opportunity awaiting further research.

### ***Supplemental $O_2$ and $CO_2$***

Several studies have demonstrated a salutary effect of supplemental  $O_2$  in patients with idiopathic central sleep apnea and patients with CHF-CSR [70]. Several potential mechanisms may explain the stabilizing effect of supplemental oxygen on respiration. Oxygen dampens peripheral chemoreceptor responsiveness and minimizes the subsequent ventilatory overshoot. In addition, prolonged hyperoxia stimulates respiration, perhaps by elevating cerebral  $PCO_2$  by the Haldane effect. Acute administration of oxygen is associated with diminished propensity to develop central apnea in normal subjects during sleep [71]. While long-term clinical trials are lacking, supplemental oxygen therapy is a promising adjunct for central apnea, especially in patients with CHF. Likewise, supplemental  $CO_2$  abolishes central apnea in patients with pure central sleep apnea, by raising  $PCO_2$  above the apneic threshold [72, 73]. However, this therapy is not practical given the need for a closed circuit to deliver supplemental  $CO_2$ .

### **Approach in Selected Clinical Syndromes**

The heterogeneity of central sleep apnea dictates individualized treatment approach, including optimal treatment of underlying medical conditions and attention to potential medication effects. A trial of nasal CPAP in the sleep laboratory is warranted to ascertain the magnitude of improvement with CPAP alone. The use of BPAP in a pressure support mode is likely to aggravate the severity of central apnea, unless accompanied by a backup rate. ASV may be beneficial in patients with CSR secondary to CHF who do not respond to nasal CPAP alone. Supplemental  $O_2$  may be beneficial in patients with central apnea that persists on nasal CPAP, especially in patients with CHF-CSR.

### **Summary**

The pathogenesis of central sleep apnea varies depending on the clinical condition. Sleep-related withdrawal of the ventilatory drive to breathe is the common denominator among all cases of central apnea, whereas hypocapnia is the final common

pathway leading to apnea in non-hypercapnic central apnea. The pathophysiologic heterogeneity may explain the protean clinical manifestations and the lack of a single effective therapy for all patients.

## Summary of Keypoints

- Central sleep apnea is not a single clinical entity; instead, it is a manifestation of breathing instability in a variety of clinical conditions. Central apnea syndrome occurs may be present in a diverse group of conditions including heart failure and obstructive sleep apnea.
- Central apneas is caused wither by hyperventilation or hypoventilation. Hypocapnia is the most potent and ubiquitous trigger of central sleep apnea. Central apnea rarely occurs as a single event; instead, it manifests by cycles of apnea/hypopnea alternating with hyperpnea.
- Central apnea is classified into the following specific categories according to the ICSD-2: (1) Primary Central Sleep Apnea, (2) Central Sleep Apnea Due to Cheyne–Stokes Breathing Pattern, (3) Central Sleep Apnea Due to Medical Condition Not Cheyne–Stokes, (4) Central Sleep Apnea due to High Altitude Periodic Breathing, (5) Central Sleep Apnea Due to Drug or Substance use. The underlying mechanisms influence the choice of therapy including optimization of medical therapy in central apnea associated with other conditions such as heart failure, hypothyroidism, or acromegaly.
- Advanced age, male gender, post-menopausal state in women and sleep–wake transition are physiologic determinants of central apnea. In contrast, central apnea is less common in REM sleep. Medical conditions which are associated with higher risk of central sleep apnea include CHF, CVA, Chronic narcotics users, acromegaly, chronic renal failure, and hypothyroidism.
- Clinical features are a combination of sleep apnea features and co-morbid conditions. The diagnosis requires nocturnal polysomnography. Specific therapeutic options include positive pressure therapy, pharmacologic therapy, and supplemental oxygen. Nasal CPAP is the recommended initial treatment of choice.

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# Chapter 13

## Insomnia: Etiology, Clinical Manifestations, and Morbidity

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**Keywords** Insomnia • Predisposition • Stress • CBT-I • Pathophysiology • Treatment • Comorbidity

### Introduction

Insomnia is a serious public health concern with high rates of patients presenting to both general and specialty care clinics with sleep disturbance as a complaint. In clinical settings, the prevalence of insomnia-related symptoms is much higher than in the general population and is attributable to increased medical and psychiatric disorders [1]. Patients with chronic obstructive pulmonary disease (COPD) have a particularly high prevalence of insomnia [2], and insomnia has considerable implications for pulmonary function in those with COPD and other respiratory disorders [3]. Insomnia is also an under recognized and under treated problem. Partly due to a lack of training in the recognition and management of sleep disorders [4]. Insomnia has a significant negative impact on diverse functional outcomes including fatigue, increased risk for accidents, impairments in memory and attentional processing, and increased risk for depression and substance use. This chapter details the diagnostic criteria for insomnia, characteristics of its symptomology, medical and psychiatric co-morbidity, pathophysiology, as well as individual and societal consequences. While the non-specific nature of insomnia symptoms have contributed to

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the variability in diagnosing and treating an insomnia disorder, it is important for the pulmonologist to recognize and treat this common medical condition.

The National Institutes of Health State-of-the-Science conference brought to attention the fact that insomnia is most often co-morbid with other medical and psychiatric conditions [5]. However, while previously defined as a symptom secondary to another disorder, insomnia is now considered a disorder requiring direct treatment. Thus, there has been a shift in conceptualization away from “secondary insomnia” to the term “co-morbid insomnia.” The reasons for this shift include: (1) the difficulty in accurately determining the cause of the sleep disturbance or its misattribution, (2) the increasing recognition that even when a presumed cause of insomnia is adequately addressed, significant sleep disturbance often remains, and (3) in many cases the insomnia predates the comorbid disorder. In contrast to co-morbid insomnia, primary insomnia is a term reserved for instances where insomnia exists in isolation [5]. Co-morbid insomnia is most commonly observed in medical practice and therefore is a key focus of this chapter.

Medical conditions that often occur in association with sleep disturbance include arthritis, heart disease, hypertension, diabetes, stroke, cancer, breathing disorders, and menopausal symptoms [6]. The most commonly occurring pulmonary disorders that coexist with insomnia are COPD and asthma.

COPD, a slowly progressive condition causing inflammation in the small airways and lungs [7], is frequently associated with dyspnea [2] and often leads to fragmented sleep with frequent arousals due to both respiratory stimulant medications such as the methylxanthines, as well as the underlying disease processes [8]. In one population-based study, 32.1% of patients with COPD reported difficulty falling asleep and 47.3% also reported frequent awakenings [6]. These reported sleep difficulties are significantly greater than those without COPD and similar to those with heart disease and neurological disorders [6]. In clinical samples more than 50% of patients with COPD report at least some insomnia symptoms [2]. In terms of having an insomnia disorder, 24.7% of patients with COPD met criteria for an insomnia diagnosis, compared with 9.9% of those without the disorder [9]. There are minimal differences in objective measures of sleep with patients with COPD having similar sleep latency and sleep efficiency (SE) compared with controls [9]. However, those patients who meet the diagnostic criteria for insomnia had a mean SE of 75.5%, significantly less than controls or patients with COPD not meeting diagnostic criteria. This emphasizes the fact that COPD is more likely to be a trigger for insomnia in vulnerable individuals rather than the cause of insomnia. Furthermore, the finding that sleep disturbance becomes more severe with advancement of the disease [10] emphasizes the importance of taking a complete sleep history from patients with COPD and considering polysomnography (PSG) particularly in those who may be at high risk for a sleep-related breathing disorder or to document the severity of sleep disturbance using objective measures [8]. It also raises the question as to the impact of insomnia on COPD severity. In terms of asthma, one recent population-based study found that 26.7% of patients

with asthma reported often having difficulty falling asleep and 37.7% also reported frequent awakenings [6]. The prevalence of patients with asthma meeting criteria for insomnia is only slightly higher at 15% than the general population prevalence of 10.1% [9]. Laboratory measures show their SE and sleep latency to be within the normal range ( $86.73 \pm 14.6$ ). Even in samples of patients with asthma where those with insomnia were compared to those without insomnia, minimal polysomnographic differences (sleep latency =  $29.7 \text{ min} \pm 3.8$  vs.  $26.1 \text{ min} \pm 1.4$ ; SE =  $83.6\% \pm 1.9$  vs.  $84.0\% \pm 0.4$ ) were found [9]. It is possible that brief arousals from sleep in patients with asthma may go undetected using traditional PSG or that more severe sleep disturbance may be present in a subset of patients with asthma who are untreated or are particularly severe. Future research in this area is warranted examining both objective measures and insomnia-related symptoms across a range of asthma severity and treatments using non-traditional measures of sleep continuity.

Despite the strong association between insomnia and medical conditions, the most prevalent co-morbidity is with psychiatric disorders, most commonly depression. In several large-scale prospective studies, insomnia is a significant risk factor for the future development of depression [11–13]. Although the directionality between insomnia and mental conditions, such as depression, has been debated, insomnia can clearly be viewed minimally as a prodromal risk factor for depression. Within sleep clinics, insomnia comorbid with a mental disorder is the most common comorbidity and is more prevalent in middle aged populations and in women [14]. Insomnia is also one of the first reported symptoms of a mental disorder, and even after a depressive episode, sleep disturbance is among the most common residual symptoms [14]. Both pharmacological and behavioral treatments of insomnia have been shown to augment the antidepressant response of SSRIs. However, research is needed to determine if continuing improvement in insomnia can prevent relapse of depression. Finally, long-term longitudinal studies are needed to determine if treatment of insomnia can prevent incident depression. Nonetheless, as insomnia is often under-diagnosed and under-treated, the link between insomnia and mental disorders emphasize the need for clinicians to identify and appropriately target insomnia symptoms as well as the primary condition is particularly important in the treatment of patients with pulmonary diseases as they have been shown to have a higher prevalence of depression. Appropriate psychiatric evaluation is a necessary component in evaluating any patient with insomnia.

Insomnia can typically be managed effectively by the primary care physician. However, sleep disturbance is also a common presenting symptom in patients with other primary sleep disorders such as restless legs syndrome, sleep-related breathing disorders, and periodic limb movement disorder [15]. Thus, it is important for non-sleep specialists to be able to identify patients who are at high-risk for these conditions and provide appropriate therapeutic intervention and/or referral for a sleep evaluation.

**Table 13.1** DSM-IV-TR diagnostic criteria for primary insomnia

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The predominant complaint is difficulty initiating or maintaining sleep, or non-restorative sleep, for at least 1 month
The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, generalized anxiety disorder, a delirium
The disturbance does not occur exclusively during the course of another mental disorder (major depressive disorder, generalized anxiety disorder, a delirium)
The disturbance is not due to the direct physiological effects of a substance (drug abuse, medication) or a general medical condition

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## DSM – IV

The DSM-IV defines primary insomnia as follows: (1) a complaint of difficulty initiating or maintaining sleep or non-restorative sleep that persists for greater than or equal to 1 month; (2) clinically significant distress or impairment in social, occupational, or other important areas of daytime function for which causation from other sleep, medical, and psychiatric disorders is ruled out; (3) the sleep disturbance must not occur exclusively during another sleep or mental disorder and is not due to the physiological effects of a substance or a general medical condition (Table 13.1). Individuals with insomnia often report more than one nocturnal symptom and also vary in type, frequency, and severity of the symptom. It is important to note that, the specificity and severity of the insomnia symptom can vary during the clinical course.

## ICSD – II

In the International Classification of Sleep Disorders [16], all insomnias are appropriately grouped together as a distinct sleep disorder category with different variants [16]. Each subtype must meet the following criteria: (1) adequate sleep opportunity (historically), (2) persistent difficulty sleeping (initiation, duration, consolidation, or quality), and (3) associated clinical dysfunction such as fatigue, attention deficits, memory impairment, mood disturbance, reduced motivation, or excessive worrying [16].

Frequency, severity, and chronicity are all important dimensions of insomnia. However, their importance in terms of diagnostic or therapeutic guidance has been debated along with quantitative cutoffs used to make a diagnosis or categorize severity [17]. A majority of insomnia clinical trials have defined insomnia with sleep-onset or maintenance symptoms occurring three nights per week with the criterion of 30 min or more for sleep initiation and 45 or more minutes for the amount of wake time after sleep onset [17, 18].

Edinger et al. used sleep log data to determine the optimal frequency and severity criteria that differentiates patients with insomnia from normal sleepers.

A relationship was found between severity and frequency of insomnia where the optimal frequency criteria decreased as the symptom severity increased and vice versa. Therefore, as both are clinically significant, a clinician could choose to diagnose based on a higher frequency (e.g.,  $\geq 3$  nights per week) and lower severity (e.g.,  $< 30$  min), or a high severity (e.g.,  $\geq 60$  min) and low frequency (e.g., 1 night per week). For example, a report of greater than 20 min for sleep latency occurring four or more nights per week was similar in predictive value compared with a sleep latency of 60 min or more once per week. Nonetheless, one should be cautious in the sole use of specific quantitative sleep parameter criteria for insomnia diagnoses as daytime impairment criteria have been underutilized and clinically underemphasized both in terms of determining insomnia severity as well as therapeutic efficacy [18]. Thus, an alternative approach would be to determine appropriate sleep symptom severity in relation to the degree of daytime impairments. An interesting line of inquiry in relation to quantitative criteria, which deserves further exploration, is whether such criteria remain stable across time and different relative to some other insomnia phenotype. For example, person A has severely disturbed sleep once per week, while person B has moderate-to-mild insomnia every night. If insomnia phenotypes such as this exist, it is important to explore their relationship to morbidity. Large-scale studies are needed in order to define appropriate quantitative criteria for these insomnia symptom domains.

There are a few longitudinal studies concerning the course and duration of insomnia. One 10-year longitudinal study utilizing 2,602 men aged 30–69 conducted from 1984 to 1994 found that the prevalence of insomnia increased with negative lifestyle factors and medical disorders [19]. The prevalence of insomnia had increased over 10 years; however, the increase was most noticeable in the 30–40 year old age group. Of 266 with insomnia in 1984, 44% continued to report insomnia symptoms in 1994, emphasizing the chronic nature of this disorder [19].

Assessing duration in insomnia is a critical component in the diagnosis of an insomnia subtype. Acute insomnia, for example, has an identifiable stressor and is relatively short in duration, typically lasting a few days to a few weeks and no longer than 3 months. This type of insomnia has clear specific stressors, which can be psychosocial, psychological, physical, or environmental, and includes difficulties with interpersonal relationships, occupational stress, loss and bereavement, a new medical disorder, or relocation. These individuals will most likely complain of daytime sleepiness or fatigue as an important symptom [16]. The 1-year prevalence of transient insomnia is 15–20% for adults [16], the most common individuals being women and older adults. Associated symptoms include sleep disturbance (primary feature) as well as worry, anxiety, sadness, depression, physical symptoms, impaired concentration and irritability attributed to either the stressor or the sleep disturbance. Alcohol, drugs, or self-medicating, worrying and poor sleep practices can further perpetuate the symptoms. PSG is not routinely necessary for a diagnosis of insomnia. When present, PSG measures may show prolonged sleep latency, increased number and duration of awakenings, short sleep time, and reduced SE [9, 16].

## Prevalence and Risk Factors of Insomnia

Insomnia is a common condition, with a prevalence of occasional or intermittent insomnia at 30–40% of the general population and chronic insomnia at 10–15% [20–23]. However, differences in diagnostic criteria influence prevalence data. Daytime consequences are of great importance, and with this criterion included, insomnia prevalence may be less [22]. Rates of insomnia are much higher in both psychiatric and clinical populations, as previously discussed, and exceeds 50% in selected populations (e.g., major depressive disorder) [23, 24].

The prevalence of insomnia is higher in women compared with men [25]. A meta-analysis investigating sex differences has shown that insomnia is approximately 1.4 times more common in women and this ratio increases with age. This may be accounted for by several factors: menopause, menstrual problems, and higher rates of medical co-morbidities associated with insomnia (e.g., depression and pain disorders). For example, in a National Health Interview Survey, it was found that among women aged 18–55, 31% who had menstrual-related problems had insomnia [26].

Studies regarding the effects of race on insomnia risk have found that older age-matched African Americans have less prevalent insomnia symptoms when compared with European Americans, but this trend is reversed in the college age group [27]. This relation between age and race is complicated by additional findings in which a higher prevalence of insomnia symptoms among US-born African Americans than among the Caribbean-born African Americans [28], and that there may be a higher incidence among older African American women (19%) than men (12%) and European Americans (14%) [29]. These results suggest that the influence of race on insomnia risk is complicated by a variety of factors including age, co-morbidities, sex, and socioeconomic status [30].

Sleep disturbance in childhood may result from sleep-related breathing disorders, parasomnias including nocturnal enuresis, sleep walking, and sleep disorders related to medical conditions or medications. However, the prevalence of insomnia in children is unknown. A large-scale study found higher prevalence of insomnia in adolescent girls (age range 11–14 years) compared with boys [31]. This finding implicates the onset of the menstrual cycle [32] as a contributing factor. The association between menses onset and insomnia might also be explained by hormonal changes in the levels of testosterone and estrogen (Angold 1998, Refs. 41–44 in Johnson et al. [32]). Insomnia is also more prevalent among adolescents aged 13–16 compared with younger groups and the risk for insomnia was higher in girls than in boys, but only after the onset of menses [32]. Among adolescents with sleep difficulties, the most common complaints were difficulty initiating sleep (68.5%), non-restorative sleep (48.1%), and difficulty maintaining sleep (26.2%). The onset of menses in girls created 2.75 times increased risk for insomnia. The relationship between insomnia and pubertal development is complex because of biological and social changes that occur at the time of menses [32].

Aging is associated with sleep fragmentation, increased arousals, and more frequent awakenings. Individuals over the age of 65 are more likely to report fragmented sleep, difficulty falling back to sleep after nocturnal awakenings,

frequent early morning awakenings, and non-refreshing sleep [33]. Insomnia is also more prevalent and complex in the elderly. The prevalence of chronic insomnia increases from 25% in the adult population to 50% in the elderly [34]. Data from the National Sleep Foundation shows that, 67% reported experiencing one or more sleep problem, and 48% reported at least one insomnia symptom at least a few times per week [35]. In the elderly, insomnia complaints are also more common in women [36]. Insomnia in the elderly is associated with significant daytime consequences, including increased risk of cognitive impairment, increased fall, and higher mortality risk.

More than 1/3 of adults over the age of 65 fall each year, making falls one of the leading causes of injury-related deaths [37] and the most common cause of injuries and trauma-related admission to hospitals [38]. Falls can result in hip fractures which limit mobility and function [39]. Previously it was thought that hypnotic use for insomnia was a significant predictor of falls. However, it is now known that insomnia produces a 90% increased risk for falls, as compared with hypnotic use which is associated with a 29% increased risk [40]. Medication use is one of the most significant causes of falling, with benzodiazepines (especially those used during the day), sedative-hypnotics, cardiac medications, antidepressants, neuroleptics, and use of multiple medications simultaneously being associated with increased risk of fall. This must not be overlooked because complications include fractures of the wrist, hip, vertebrae, or subdural hematoma [41]. Physicians should be cautious of medications that may increase the risk for falls, such as long-acting hypnotics (half life >6 h), where residual effects are more prominent and in turn lead to slower response times and balance problems well into the wake period [36].

In a study focusing on mortality risk, a 2-year follow-up on hospitalized geriatric patients found that the presence of insomnia symptoms and specifically sleep onset delay was associated with a higher mortality rate, indicating that insomnia may be an independent risk factor for survival [42]. Insomnia and difficulty initiating sleep have also been associated with coronary artery disease mortality in men [43]. Additionally, a study by Leppavuori et al. [44] found the prevalence of post-stroke insomnia complaints to be 56.7% in a population of 486 stroke patients aged 55–85. Given that the consequences of a stroke disable an individual and insomnia can further debilitate daytime functioning, insomnia complaints should be taken seriously and treated independently in medically ill patients.

## Pathophysiology of Insomnia

Insomnia is often conceptualized as an underlying predisposition with precipitating and perpetuating factors. Precipitating factors trigger insomnia in vulnerable individuals while perpetuating factors maintain the insomnia even after the trigger has dissipated. This is termed the 3-P model of insomnia, developed by Spielman in 1986. Ultimately, optimal treatment involves identifying and addressing each facet of the disorder.

In terms of the predisposition to insomnia, Drake and Roth have hypothesized that an important aspect of vulnerable individuals is pre-morbid sleep-reactivity to stress [45]. Sleep reactivity is a term used to delineate an elevated response of the sleep system to challenges known to disturb sleep. Over the past decade studies have found increasing support for this hypothesis. For example, a measure of sleep reactivity (Ford Insomnia Response to Stress Test) has been shown to predict the degree of sleep disturbance (both PSG and self report) to diverse challenges, such as a first night effect in the sleep laboratory [46] and the disruptive effect of low-dose caffeine administration [45]. Reactivity is higher in insomniacs [47] and has been shown to display substantial familial aggregation [48]. More recently a preliminary analysis of sleep reactivity using a large twin cohort has shown a significant genetic component providing evidence for more than 30% heritability of sleep reactivity [49]. Additional studies investigating the predictive value of sleep reactivity are needed before definitive conclusions regarding this potential predisposing factor can be made.

Regardless of the exact nature of the predisposition, the interaction between triggers and vulnerability may cause certain individuals who experience stressors to have an increased sleep response in terms of magnitude, duration, and/or frequency which eventually leads to insomnia [45]. Onset of insomnia can be triggered by many different medical, psychiatric, psychosocial, or environmental factors [50]. Several psychosocial stressors, including marital difficulties, divorce, separation, and dysfunctional relationships within the family have been linked to the onset of insomnia [50]. Work-related sources of stress that were identified as precipitating insomnia included conflicts with a supervisor, interpersonal relationships, workload, and financial strain. A vicious cycle may develop whereby stress at work develops into disturbing and intrusive thoughts when a person is trying to sleep and is unable to relax. This stress may also be cumulative, where sleep problems are produced only after the accumulation of stress over time. Ongoing financial strain has been measured as a form of chronic stress and has shown significant importance in the elderly population [51]. Persistent financial strain was associated with sleep continuity disturbances in a sample of community elders between the ages 61 and 85. Elders experiencing ongoing financial strain took longer to fall asleep, and had an average of 88 min of wake after sleep onset (WASO), as compared to 69 min among elders who did not self-report financial strain. While precipitating events have been shown to vary with age, they are fairly consistent across genders [50]. Age of insomnia onset was related to different categories of precipitating factors; precipitants related to work and/or school were more common when the onset of insomnia occurred earlier in life, whereas health factors were associated with insomnia later in life.

Maladaptive behaviors such as poor sleep habits, cognitive arousal, ruminating, worrying, or catastrophizing often serve to maintain the insomnia despite the disappearance of an initial precipitating factor [13]. For example, insomnia could be maintained by habits such as inappropriate caffeine or alcohol consumption,



increased time in bed, napping, or other poor sleep hygiene practices, even after the precipitating stimuli has been removed. One study has shown that individuals with insomnia are more likely to engage in inappropriate sleep practices that may exacerbate or perpetuate sleep disturbances [47]. These behaviors include smoking, alcohol use, and compensatory sleep (naps and sleeping in on the weekends). Not only was the prevalence of smoking and alcohol use higher in insomniacs compared with controls, but insomniacs were also more likely to smoke within 5 min of bedtime and use alcohol to induce sleep within 30 min of bedtime. Some insomniacs choose to self-medicate with alcohol in order to induce or improve their sleep and of these 67% perceived it as effective in alleviating symptoms, consistent with the widespread inappropriate use of alcohol to help sleep [52]. This may lead to an increased risk of dependence and tolerance requiring larger amounts of alcohol in order to reach similar effects on sleep [53]. However, alcohol fragments sleep, particularly during the second half of the night [54]. Such fragmentation may not be detected by the individual. Compensatory daytime napping may become a factor, which decreases an individual's homeostatic sleep drive at night, subsequently producing sleep disturbance. Insomniacs have been shown to "sleep in" more frequently, possibly as an attempt to compensate for their disturbed sleep at night [47].

## Clinical Assessment

### *Sleep History*

It is important to determine whether the patients' habits are contributing to their insomnia. A physician should determine usual work hours, and whether the patient spends appropriate time in bed relative to sleep time. A two-week sleep diary is one of the best ways to have a patient keep track of their bedtimes, wake times, quantity and quality of sleep, as well as other factors such as alcohol, tobacco, and medication use. The National Sleep Foundation is a resource where a sleep diary can be found for clinical and research use ([www.sleepfoundation.org](http://www.sleepfoundation.org)). Spending enough time in bed may improve sleep, considering no other pathologies are present [55]. However, in most cases, patients with insomnia are unable to attain 7–8 h of sleep despite adequate time in bed and spending too much time in bed further fragments sleep. Prescription drugs, pain medications, alcohol, and caffeine can all disrupt normal sleep and complicate the diagnosis [55]. It is important to ask the patient about their sleep environment and any other factors that could be interfering with their sleep such as excessive cold, heat, light, or noise. Other clinical questions are also useful including: does a patient take naps and as a result, feel more alert? What types of settings cause them to doze? [56, 57].



## ***Medical History***

In terms of pulmonary conditions, patients with COPD often present with the complaint that their sleep is fragmented and they have difficulty falling back to sleep. Their PSGs have shown increased time in stage 1 sleep, increased arousals, and decreased REM, often related to hypoxemia or hypercapnic events.

## ***Psychiatric History***

It is important to be aware of potential psychological disorders especially depression and anxiety, which often present co-morbidly with insomnia. Psychological stress has also been shown to play a significant role in the onset and maintenance of primary insomnia in adolescents, and young adults [55]. To help in identifying patients who have personality disorders, a screen for psychological disorders can be used. A drug screen is also important in ruling out drug abuse which may have profound effects on sleep [56, 57].

## ***Family History***

It is suggested that patients who have insomnia have a higher incidence of relatives with sleep disturbances, with the mother most commonly affected. It is very important to discern whether there is any family history of insomnia or medical or psychiatric disorders to understand all familial factors surrounding the disorder as an indicator of potential underlying predisposing factors. Of equal relevance are the patient's psychosocial history, occupational and school performance, amount of interpersonal support, and presence of psychosocial stressors, all of which can precipitate insomnia [56]. A patient's significant other is also a valuable resource for information about their bed partner's symptom frequency, duration, severity, and daytime impairment as well as the presence of breathing problems, periodic limb movements, or parasomnias during sleep.

## ***Medication History***

Many different medications can contribute to sleep complaints and daytime consequences. A thorough assessment of all prescription and non-prescription medications, CNS stimulants (including many weight loss supplements), and herbal remedies can play a significant role in perpetuating or exacerbating the insomnia. Prescription medications used to treat COPD, asthma, allergies, hypertension,

epilepsy, psychotic disorders, anxiety, and pain if present should be important considerations in the evaluation [57, 58]. A physician needs to assess the dosage, type, frequency, and timing of usage and consider the timing of onset of insomnia complaints in order to determine whether continued use is necessary or timing of dosing can be modified to minimize the sleep disruptive effects of the medication [56].

A significant portion of the insomnia assessment and interview should be focused on the evaluation of medical disorders, psychiatric conditions, other sleep disorders, and substance use, all of which are commonly co-morbid with insomnia. This will help determine whether the identified complaint and condition is a predisposing, precipitating, or perpetuating factor.

Different types of behavioral insomnia treatments include relaxation therapies, stimulus control, sleep restriction, paradoxical intention, improving sleep hygiene, and cognitive behavioral therapy. There are also pharmacological treatments for treating the co-morbid insomnia conditions. Cognitive-behavioral insomnia treatment and pharmacotherapy with benzodiazepine receptor agonists have both been proved effective [30, 59]. Please refer to Chapter 15 in this volume for further information.

As insomnia is a symptom-based diagnosis, PSG is usually not necessary. However, PSG is useful if there is suspicion of another primary sleep disorder, such as apnea sleep-related breathing disorder. Individuals with chronic insomnia may still have PSG sleep that is within normal limits ( $>85\%$  SE and  $<30$  min sleep latency). Therefore, polysomnograms are most important in ruling out obstructive sleep apnea, periodic leg movements, and other primary sleep disorders in patients.

Self-reported measurements of sleep are effective, take minimal time, and are useful in a variety of medical settings. Sleep diaries are considered a standard self-reported measure of insomnia with a recommended collection time of two weeks in order to obtain reliable information regarding sleep patterns. Sleep diaries typically include sleep onset latency, time of awakening during the night after sleep onset (WASO), number of awakenings during the night, total time in bed (TIB), total amount of sleep (TST), and SE calculated from TST/TIB as a percentage. Estimates of naps, types of medication, caffeine, alcohol, nicotine use, and ratings of sleep quality can be included. A sleep diary is especially valuable when a circadian rhythm disorder is thought to be comorbid with the insomnia. Insomnia severity scales such as the insomnia severity index can help the clinician assess the severity of the insomnia as well as the effectiveness of the treatment [60].

When objective measures of sleep are desired in patients with insomnia, one useful method of assessing sleep is actigraphy, which is a small movement activated device attached to a patient's dominant wrist [61]. The algorithm of movement and non-movement has been shown to predict PSG within 93% accuracy for normal subjects. Minutes of non-movement are recorded as sleep time and SE reported as minutes of non-movement divided by TIB. Actigraphy has also been shown to detect changes in sleep variables in response to treatment, and may be more accurate than sleep diaries due to its promotion of treatment compliance at home and high reliability [62]. Thus, actigraphy can be a useful tool for assessing habitual sleep patterns as well as night-to-night variations in sleep. However, the accuracy of sleep onset calculated by actigraphy has been questioned; as individuals lie motionless in

bed actigraphy may score wake as sleep. Thus, caution should be used when evaluating this measure based on actigraphy alone. Actigraphy in determining sleep onset has been questioned and caution in evaluating latency is warranted, as individuals may lie motionless in bed where actigraphy may inaccurately score wake as sleep [62].

## Functional Outcomes Associated with Insomnia

Sleep plays a vital role in the regulation of endocrine functions and glucose metabolism. Reduced sleep duration and/or poor quality sleep may be linked to an increased risk for diabetes mellitus and insulin resistance [63]. Insomnia with short sleep duration (<5 h) has also been associated with increased risk of hypertension (OR=5.12 and 95% C.I. 2.2–11.8) [64]. Therefore, insomnia in combination with short sleep appears important in terms of cardiovascular risk [64]. The ability to consolidate newly encoded memory traces during sleep is also reduced in patients with insomnia [65]. Additionally, primary insomnia is associated with decreased sleep-related consolidation of declarative memory [66]. In terms of quality of life, studies have shown higher divorce rates, reduced job satisfaction [67], and reduced family and social interaction among people with insomnia [68]. In a study by Leger et al. [67], insomniacs had an almost twofold higher rate of absenteeism as compared to normal good sleepers; as measured during a 2-year period, 50% of insomniacs and 34% of good sleepers had an absence during this time. Insomniacs also have higher rates of hospital and medical services utilization, including visits to healthcare professionals, medical examinations, medications, and hospitalizations [67]. The individual cost to society has been estimated at \$552 per year in work-related absences and \$4,154 in reduced productivity [69], with direct and indirect costs exceeding 30 billion annually [1, 70]. Notably, the costs of untreated insomnia are significantly greater than the direct costs associated with treatment. Leger et al. [67] also found that the annual loss of insomnia-related productivity is 27.6 days per year vs. 2.8 days for good sleepers, a 10:1 ratio. Finally, insomniacs have been found to have a higher incidence of major accidents, are less likely to report being responsible for the accident, and report longer absences after the accidents as compared to good sleepers [67].

## Conclusion

Insomnia is a common and complex disorder, arising from a multitude of psychosocial and biological factors. It is under recognized in medicine and yet is significant in terms of the consequent health effects, quality of life, social, occupational, and mental health components [71]. Insomnia is also associated with an increased risk for psychiatric illness and other adverse health problems, increased falls and

accidents, greater healthcare utilization, and overall costs to society. In the clinical setting, there is a need to standardize the assessment instruments, diagnostic criteria and evaluation strategies. The initial identification and management of insomnia would be greatly improved by the increased use of validated brief assessment tools, outcome measures, and algorithms for treatment within and outside the sleep clinic and pulmonary care settings.

## Summary of Keypoints

- Insomnia is a serious public health concern with a high prevalence of co-morbid conditions and serious societal and health consequences.
- Many pulmonary conditions produce sleep disturbance and may contribute to the development of chronic insomnia in predisposed individuals.
- Affects women approximately 40% more than men.
- The pathophysiology of insomnia includes Spielman's 3-P Model, the interaction between predisposition, precipitants, and perpetuating factors and maintaining factors.
- Maladaptive behaviors include caffeine and alcohol consumption, poor sleep hygiene habits, and their association with reduced and fragmented sleep.
- Assessment of a patient with insomnia should include a sleep history, medical history, psychiatric history, family history, and the use of self-reported measures such as a sleep diary.
- Negative functional outcomes associated with insomnia can occur in terms of memory, absenteeism, and productivity.

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# Chapter 14

## Management of Insomnia

Luisa Bazan, Thomas Roth, and Christopher L. Drake

**Keywords** Neuromuscular disorders • Insomnia • Interstitial lung disease • Chronic obstructive pulmonary disease • Asthma • Nocturnal hypoxemia • Hypnotics

### Introduction

Insomnia is defined as a “subjective report of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep, and that results in some form of daytime impairment” [1]. It is one of the eight major categories of sleep disorders in the *International Classification of Sleep Disorders*, second edition (ICSD-2) [2]. Symptoms of insomnia may occur in association with comorbid disorders or other sleep disorders, such as sleep-related breathing disorders, circadian rhythm sleep disorders, and sleep-related movement disorders [1, 3]. However, it is increasingly recognized that insomnia is a primary disorder and independent treatment of the sleep disturbance is warranted even in the context of other common comorbidities such as depression or respiratory disorders [4].

According to population-based studies, more than 30% of adults report sleep disruption, while approximately 10–20% have associated symptoms of daytime impairment or distress consistent with the diagnosis of insomnia [5, 6]. It is estimated that the majority of people with insomnia (approximately 75–90%) have comorbid medical disorders, such as conditions causing hypoxemia and dyspnea, gastroesophageal reflux disease, pain conditions, and neurodegenerative diseases [3, 7, 8].

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It has been reported that insomnia with objective short sleep duration is associated with a significantly increased risk for hypertension and type 2 diabetes [9, 10]. Studies have also shown increased mortality in males with insomnia symptoms and objective short sleep duration (less than 6 hours of sleep) [11]. Based on this information, it is possible to infer that patients with respiratory disorders, such as chronic obstructive pulmonary disease (COPD), with comorbid insomnia, are at higher risk for developing hypertension and diabetes and worse mortality.

Meissner et al. evaluated the prevalence of sleep complaints in a group of general medical patients admitted to a Veterans Affairs tertiary care medical center. A total of 222 consecutive adults completed the questionnaire. Of these, 105 patients (47%) reported either insomnia, excessive daytime somnolence, or both. Of 75 patients (34%) who reported insomnia, a third were taking hypnotic medication. Despite this, none of the patients with insomnia had any mention of the sleep difficulties in their medical record [12]. This study demonstrates that physicians in general, often fail to ask patients about their sleep. Not doing so increases the risk of missing sleep disorders where effective treatment could have the potential to improve overall prognosis and quality of life.

This lack of attention to sleep disorders can be traced back to medical school curricula. A national survey conducted by Rosen et al. in 126 accredited medical schools in the United States showed that less than 5% of medical schools offer 4 or more hours of didactic teaching on sleep, most of which consists of fourth year elective experiences. More than two-thirds of the survey respondents stated that current sleep education is inadequate and that additional time should be devoted to this area [13]. These studies emphasize the rationale for education regarding the treatment of insomnia in pulmonary settings.

Treatment of insomnia can be challenging, particularly when multiple comorbidities are present. Cognitive behavioral therapy (CBT) with or without concomitant pharmacologic therapy is recommended [1]. Although most pulmonologists are adept at treating OSA, adequate expertise to treat insomnia, especially behavioral approaches, may be limited. Sixty physicians participated in an interactive survey at the 1998 American College of Chest Physicians (ACCP) annual meeting. Performance on test questions about sleep-related breathing disorders was better than on questions about “non-breathing related” sleep disorders. The respondents recognized a need for supplemental training, familiarity with the technical aspects of sleep medicine, and access to other specialists in the field [14]. Thus, despite extensive training in sleep-related breathing disorders, pulmonary physicians can benefit from additional training on the diagnosis and treatment of non-breathing related sleep disorders such as insomnia.

In this chapter, we will review the current data on pharmacologic and non-pharmacologic treatments for insomnia focusing on the potential importance to pulmonary medicine specialists.

## Control of Breathing During Sleep

Treating insomnia comorbid with respiratory disorders can be complex. Sleep in patients with lung disease is affected by their pulmonary symptoms (e.g., cough, shortness of breath), baseline hypoxemia, baseline hypercapnea, as well as medications utilized for the treatment of pulmonary disorders. The current treatment modalities for insomnia include behavioral vs. pharmacological therapy. If pharmacological therapy is considered in a patient with an underlying pulmonary disorder, it is important to have adequate understanding of the respiratory physiology during sleep and the effects of the different therapeutic agents on control of breathing, since patients with underlying lung disease have limited reserve to overcome further challenges to ventilation during sleep.

In this chapter we will review the effects of hypnotic medications on the respiratory drive in relation to hypercapnea and hypoxemia and their effect on respiratory muscle function.

Control of breathing is affected by the state of consciousness. During wakefulness, the volitional control of breathing input from the waking state is an important stimuli to the ventilatory function. However, volitional control of breathing is abolished during sleep leading to decrease stimulation of respiratory drive. Positional changes associated with sleep also result in alterations in respiratory mechanics. Sleep has effects on breathing, including changes in respiratory control, airway resistance, and muscular contractility [15, 16].

Sleep is subdivided into two distinct states: non-rapid-eye movement (NREM) and rapid-eye movement (REM) sleep. Various aspects of respiratory control differ between wakefulness, NREM and REM sleep. The reader is referred to Douglas [17] for a review. For example, minute ventilation in healthy individuals falls during sleep due to decreased metabolism and decreased chemosensitivity to carbon dioxide ( $\text{CO}_2$ ) and oxygen ( $\text{O}_2$ ). The drop of ventilation between wakefulness and NREM sleep has been shown to be between 10 and 15%. The drop of ventilation during REM sleep has been calculated at 15–16% from the awake state [15, 18, 19].

$\text{CO}_2$  is the most potent respiratory stimulus. The end-tidal  $\text{CO}_2$  ( $\text{ETCO}_2$ ) increases by 2–3 Torr during NREM sleep with a further increase of 2–3 Torr during REM sleep. Thus, the arterial carbon dioxide partial pressure ( $\text{PaCO}_2$ ) can be up to 5 Torr higher in REM sleep than in wakefulness. The increase in  $\text{PaCO}_2$  should increase minute ventilation during sleep; however, the opposite happens. There is actually a decrease in the slope of the ventilatory response to increasing inspired  $\text{CO}_2$  during sleep. That drop is modest during NREM sleep and is greater in REM sleep. These changes are more evident in males than in females. Respiratory output in sleep, particularly NREM sleep, is significantly reduced in response to hypocapnea. The changes in chemosensitivity to  $\text{PaCO}_2$  can be related to peripheral mechanical factors or central neural factors [16, 19, 20].

In normals, both hypercapnea and hypoxia activate the sympathetic nervous system and produce arousals. The arousal threshold for  $\text{CO}_2$  is typically between 55 and 65 Torr although there is a significant variation in that range [19]. During sleep, an elevation of the  $\text{ETCO}_2$  of 15 mmHg above the level in wakefulness awakens most subjects [21]. Douglas et al. evaluated hypercapneic drive during sleep. The rise in  $\text{CO}_2$  during hypercapneic ventilatory responses (HCVR) was significantly higher during wakefulness ( $12.7 \pm 0.3$  mmHg) than during sleep (9–10 mmHg) with no difference between the mean rise in each sleep stage [20]. Berthon-Jones and Sullivan [22] reported  $\text{CO}_2$  arousal thresholds up to 6 mmHg higher in slow wave sleep (SWS) than in either stage 2 or REM sleep in male but not in female subjects.

The eucapnic hypoxia arousal threshold in healthy humans shows a marked variability in NREM and REM sleep, with subjects failing to awaken by 70% of oxygen saturation ( $\text{SaO}_2$ ). The wake-NREM and wake-REM ventilatory responses to hypoxia were significantly different; however, the NREM–REM difference was not [23]. Pappenheimer noticed that acute exposure of rats to 10.5%  $\text{O}_2$  (5,030 m altitude equivalent) during daylight hours (sleep phase) virtually abolished REM sleep and shifted the distribution of amplitudes of SWS electroencephalography (EEG) toward awake values. Similar disruption of sleep occurred during inhalation of 0.05% carbon monoxide (CO) with steady-state carboxyhemoglobin of 35%. The decreased intensity of NREM sleep during hypoxia (i.e., decreased amplitude of cortical slow waves), may explain the disparity between subjective complaints of insomnia at altitude and evaluations of sleep by direct observation or by conventional EEG [24].

Because some hypnotics suppress musculoskeletal function during sleep, and these effects vary in intensity depending upon sleep stage, it is important to understand the effects of changes in sleep state on upper airway and respiratory muscle function. NREM sleep is associated with a decline in activation of the upper airway muscles that is amplified during REM sleep. The activity of respiratory accessory muscles in the neck and chest wall is inhibited during REM sleep. REM sleep is subdivided into two periods: tonic and phasic. During REM sleep, there is tonic absence of muscle tone (i.e., muscle atonia), but the phasic period is further identified by bursts of desynchronized REMs. During these bursts of REMs, the electrical activity of the diaphragm is quite irregular and desynchronized, thus further contributing to a reduced ability of this muscle to generate force [16]. Thus, REM reduces respiratory muscle activity leading to hypoxemia and hypoventilation which can be a significant contributor to sleep complaints (i.e., nocturnal awakenings) in patients with respiratory disease.

Patients with underlying lung disease are also at risk for oxygen desaturation and increased ventilation–perfusion mismatch as a result of sleep-related hypoventilation and postural change, respectively. In response to this hypoxemia and/or hypercapnea, ventilation and respiratory effort both increase. While the arousal response to hypoxemia is not always consistent, when combined with an increased effort of breathing it can produce arousals potentially leading to reports of disturbed sleep [25].

## **Pulmonary Disorders and Sleep**

Patients with pulmonary disorders often report insomnia-related symptoms. Studies have evaluated the prevalence of insomnia as well as reports of sleep disturbances in patients with different pulmonary disorders.

### ***Bronchospastic Airway Disorders***

Patients with bronchospastic airway disease frequently report difficulties with sleep. Klink et al. reported the prevalence of sleep disturbances in a general adult population and in a subgroup of patients with chronic obstructive airway disease in the Tucson Epidemiologic Study. Patients were classified as having either asthma, chronic bronchitis alone or chronic bronchitis with asthma and emphysema. Subjects with chronic bronchitis alone and emphysema had a 53.2 and 54.6% prevalence of difficulty initiating or maintaining sleep (DIMS) and 26.2 and 28.8% prevalence of excessive daytime sleepiness (EDS), respectively, each of which was significantly higher relative to those with no airway disease (35.6 and 10.6%). Patients with chronic bronchitis and asthma showed the highest prevalence of DIMS (75%) and similar prevalence of EDS (25.2%). In patients with asthma the prevalence of DIMS and EDS was no different than in patients with no airway disease. No significant influence of smoking status was noted in any of the four groups [26]. It has been consistently shown that patients with asthma report disrupted sleep. Fitzpatrick found that 85% of asthmatics report waking up at night with wheeze occasionally, and 31% did frequently (more than 20 times/year) [27]. Turner-Warwick et al. found that among primary care patients in the United Kingdom, 74% of patients with asthma report awakening at night at least once a week, and 64% reported awakening at least 3 times a week. Even in patients that regarded their asthma as mild, 26% of them reported awakening every night [28]. In a study with cystic fibrosis patients, with an average age of 14 years old, 43.5% reported sleep onset problems, 39.1% reported sleep maintenance problem, 30.4% were noted to snore at night, and 73.9% reported daytime sleepiness. On PSG evaluation, sleep efficiency was decreased, REM latency was increased, and REM sleep was decreased relative to controls. Sleep efficiency was correlated with forced expiratory volume in 1 s ( $FEV_1$ ) but there was no correlation with minimum oxygen saturation or maximal  $ETCO_2$ . The magnitude of sleep disruption in these patients was mainly related to the severity of their lung disease, but not directly correlated with the degree of nocturnal hypoxemia or hypoventilation [29].

### ***Interstitial Lung Diseases and Sleep***

Several studies have reported disturbed sleep in patients with interstitial lung diseases (ILD) and Interstitial Pulmonary Fibrosis (IPF). Patients with ILD showed

more stage 1, less REM sleep, more arousals and sleep stage changes relative to age and gender-matched controls [22]. Patients with awake oxygen saturation less than 90% had a higher percentage of stage 1, more sleep state changes, and longer awake time than did patients with awake saturation above 90%. The apnea/hypopnea index (AHI) in patients with ILD and controls was within normal limits in this study [30]. Krishnan et al. [31] found that mean scores on the Pittsburgh Sleep Quality Index (PSQI) was significantly higher in IPF patients relative to controls, indicating poor sleep in these subjects as compared to controls.

Mermigkis et al. studied 15 patients with IPF and 15 control subjects. There were statistically significant differences between IPF patients and controls on PSG in sleep efficiency (65% vs. 78%), stage 1 sleep (18.7% vs. 7.4%), SWS (10.4% vs. 16.5%), arousal index (AI) (26 vs. 13 events/h), mean oxygen saturation (91.6% vs. 95.3%), nadir oxygen saturation during sleep (81% vs. 91%), and the percentage of total sleep time (TST) with oxygen saturation under 90% (34% vs. 0.9%). There was no significant difference in the AHI (9.2 vs. 7.1 events/h). Daytime tachypnea persisted during sleep (20.6 vs. 22.9 breaths/min (bpm), respectively). The most common complaint was daytime fatigue, reported in all cases and also confirmed by the Fatigue Severity Scale (FSS) scores. EDS, snoring, insomnia, and witnessed apneas were reported in 20, 40, 46.6, and 13.3% of the cases, respectively. Quality of sleep and daytime function were moderately to significantly impaired based on the PSQI and Functional Outcomes of Sleep Questionnaire (FOSQ), respectively. Nocturnal hypoxemia showed a significant correlation with FSS scores. The total FOSQ score was negatively correlated with TST with oxygen saturation below 90%. FSS scores were correlated with TST at oxygen saturation below 90% and mean oxygen saturation during sleep. Thus, nocturnal hypoxemia appears to be associated with a reduction in energy levels and impairment of social and physical functioning [32].

As hypoxemia has been found to correlate with daytime fatigue and interruptions of sleep at night, it raises the hypothesis that oxygen supplementation will improve sleep. Vazquez et al. evaluated the impact of oxygen on patients with ILD. The average arterial oxygen partial pressure ( $\text{PaO}_2$ ) was 51 mmHg while awake. All patients underwent two consecutive full PSGs, one breathing room air and one breathing supplementary oxygen through nasal prongs. Controls were studied for one night breathing room air. The mean  $\text{SaO}_2$  in ILD patients was 82% during sleep on room air and 94.8% on oxygen. In controls it was 92.9%. Sleep efficiency and AI were similar in patients and controls and did not change with oxygen. Thus, hypoxemia does not appear to be the cause of sleep disturbance in patients with ILD [33]. Another potential etiology of disturbed sleep in these patients is the increase in respiratory frequency while sleeping. This phenomenon has been attributed to the persistence during the sleep phase of the reflexes causing the rapid shallow breathing during wakefulness. To the author's knowledge, the evaluation of that mechanism (rapid, shallow breathing) as a potential cause of disturbed sleep has not been done.

Patients with IPF have poor prognosis and poor response to the current available treatments. Dyspnea and coughing are usually progressive and about 50% of the patients die within 3 years after diagnosis. The early recognition of sleep disturbances and its treatment should be one of the primary goals of care, since it may improve quality of life in a disease with no effective treatment. Studies to evaluate

the safety of hypnotics in this patient population are important yet, to date no studies have assessed the efficacy or safety of hypnotics in this group. Other therapeutic aspects of IPF symptoms such as cough with antitussive therapy; oxygen supplementation or non-invasive ventilation on sleep and breathing should be evaluated in controlled trials, having as a goal the improvement of sleep disturbance in these patients. The response of insomnia symptoms to CBT in this population should also be evaluated, since it can potentially be successful; CBT has been used in other disorders with comorbid insomnia with good results. Potential limitations for the application of CBT in this group of patients might be the progression and severity of their disease. However, as in the case of hypnotics, the effects of sleep restriction, one of the interventions used in CBT, and associated blunting of arousal with excessive sleepiness needs to be evaluated.

### ***Kyphoscoliosis, Restrictive Thoracic Cage Disorders, and Sleep***

Guilleminault et al. studied five severe kyphoscoliosis (KS), with four of the five having been referred to the sleep laboratory; two complained of severe daytime sleepiness, one complained of disrupted nocturnal sleep, and one was referred for concerns of obstructive sleep apnea (OSA). All the patients were found to have apneas or hypopneas (AHI between 11 and 68) associated with desaturations [34]. Sawicka et al. studied 11 subjects with non-paralytic, 10 with paralytic KS, and 9 with normal controls. The sleep evaluation did not show any difference in TST or REM percentage among the groups despite the differences in pulmonary parameters such as rise in end tidal volume and transcutaneous CO<sub>2</sub> and a reduction in oxygen saturation especially during REM sleep in KS patients [35].

Masa et al. in a group of five patients with restrictive thoracic disorders (two of them with only KS, two with KS associated to myopathy or spondyloschisis, and one with history of thoracoplasty), found a 20% (one out of five patients) incidence of insomnia after discontinuation of at least 2 months of successful non-invasive positive pressure ventilation (NIPPV) therapy. Upon comparison of the sleep data while on NIPPV and after withdrawal of NIPPV therapy, there was an increase in the number of arousals and awakenings following withdrawal which can indicate more disturbed sleep; however, the difference was not statistically significant possibly due to the small sample. A severe worsening of gas exchange was observed as well, mainly during REM sleep. The lowest oxygen saturation in REM sleep with NIPPV was 74% and without it was 47%. Patients spent only 17 min on average under 80% saturation while on NIPPV, and 212 min without NIPPV. It is possible that the sleep disturbances in patients with KS are related to the hypoxemia secondary to hypoventilation which is resolved by NIPPV [36].

Gonzalez et al. evaluated the effects of long-term NIPPV on symptoms, pulmonary function test results, sleep and respiratory muscle performance in patients with ventilatory insufficiency due to severe KS. Sixteen patients were included. Although PSG results showed no significant differences in sleep stages, sleep efficiency, number of arousals or awakenings, or TST after 6 months of treatment,

there was a significant improvement in symptoms of perceived sleep quality and daytime drowsiness quantified using a visual analog scale (VAS) before and after the initiation of NIPPV [37]. In another similar study by Brooks et al. an evaluation of the long-term effects of home mechanical ventilation (HMV) on pulmonary function, gas exchange, sleep architecture, and functional exercise capacity (6-min walk test) was performed. Seventy-four patients with KS or neuromuscular disease were included. Measurements were done upon initial evaluation before initiation of HMV and immediately after. Measurements were repeated 1–2, 5, and 8–10 years later. There were no differences on sleep efficiency or AI after initiation of NIPPV [38]. Both studies showed improvement in gas-exchanged parameters and exercise performance, respectively after initiation of NIPPV on this population. There was also an improvement in the perception of sleep quality in the first study, even though there were no changes on the sleep parameters measured by PSG, even after 10 years on NIPPV. It is possible that the poor perception of sleep quality was not related to abnormalities in the sleep pattern evaluated by PSG, but mainly to the abnormalities in gas exchanged which were improved on NIPPV. Based on that finding, NIPPV should be considered the first-line therapy for patients with KS with poor sleep quality. The studies mentioned above do not categorize the sleep complaints as either sleep initiation or sleep maintenance problems. This is unfortunate since addressing that issue can help in deciding the most adequate pharmacologic therapy.

No studies have been done in this population to evaluate the effects of pharmacological treatment for insomnia or the safety profile of hypnotics, or other pharmacologic agents such as ramelteon or doxepin. The use of sedative hypnotics can be of concern due to their potential worsening of their already very limited pulmonary function. For example, patients with KS develop shallow breathing to counteract the increased work of breathing secondary to their abnormal lung mechanics. A subsequent blunting of the ventilatory response to hypercapnea develops as well. The lower tidal volume results in increased dead space ventilation. Reduced lung volumes are associated with the closure of small airways, abnormal distribution of inspired air, and atelectasis, which all contribute to hypoxemia. Low functional residual capacity puts the patient at risk for more rapid desaturations with any level of sleep disordered breathing (SDB). Patients with KS also develop problems with control of breathing such as in patients with a history of poliomyelitis, whose disease affects the medullary centers in addition to the respiratory muscles [39]. If patients with KS develop insomnia, a very good option will be CBT since that can potentially be successful and avoids the use of pharmacological therapy. If pharmacologic therapy is decided, doxepin or ramelteon, due to their mechanisms of action, are less likely to produce worsening hypoxemia or hypoventilation, so they might be considered safer in this population. It is unclear if they will be effective, however, since no studies in this population have been published. If sleep initiation is the main complaint, then ramelteon would be a good option; if the problem is sleep maintenance, then doxepin will be the alternative. Both options should be evaluated in future studies.



## ***High Altitude Sickness and Insomnia***

Current transportation technology allows millions of people a rapid ascent to high altitudes for travel or recreation. In unacclimatized persons, failure of the body to adapt to the stress of hypobaric hypoxia may lead to cerebral and pulmonary syndromes as well as insomnia.

Acute Mountain Sickness (AMS) and High-altitude cerebral edema (HACE) refer to the cerebral disorders, while high-altitude pulmonary edema (HAPE) refers to the pulmonary abnormalities. Risk factors for developing high-altitude illness include ascending too rapidly the length of altitude exposure and acclimatization, absolute height of altitude, increased level of exertion, increased obesity, cold temperature, low pressure weather systems, increased fitness level, and personal physiologic susceptibility [40, 41].

Alterations in sleep quality have been reported at high altitude. Szymczak et al. evaluated sleep quality at high altitude using the PSQI and the Athens Insomnia Scale (AIS-8) in an expedition conducted in the Himalayas (4,524 m). PSQI scores showed that 17 (53%) of the participants experienced poor sleep quality and according to the AIS-8 criteria for insomnia cutoff score, there were 15 (47%) insomniacs. In addition, reported sleep latency increased by almost 1 h at high altitude [42]. The incidence of AMS has been studied at moderate altitude (2,000 m). Montgomery et al. [43] found that AMS occurred in 25% of subjects at 2,000 m compared to 5% at sea level.

Jafarian et al. evaluated high-altitude sleep (HAS) disturbance through the Groningen Sleep Quality Scale (GSQS) after the first night's stay at 3,500 m of altitude for 100 participants. Sixty percent of participants reported sleep disturbance (the most prevalent symptom), followed by headache in 49% [44].

Sleep studies have been performed at altitude to assess changes in sleep stages. Miller et al. studied the effects of hypobaric hypoxia equivalent to an altitude of 4,268 m in four male and four female subjects. He observed increase in light sleep (stage 1), with a decrease in stage 2 sleep and mild drop of stages 3 and 4. TST was unchanged with no significant changes in REM sleep [45]. Johnson et al. evaluated sleep architecture and its relationship to periodic breathing during incremental increases in altitude in 19 normal subjects. Overnight polysomnography was performed in 14 subjects at altitudes 0, 1,400, 3,500, 3,900, 4,200, and 5,000 m above sea level. Time spent in stage 1 increased and time spent in SWS decreased as altitude increased. Time spent in REM sleep was preserved. Sixteen subjects developed periodic breathing during sleep at one or more altitudes. The occurrence of periodic breathing increased with altitude from an average AHI of 20 events/h at 3,500 m up to 68 events/h at 5,000 m. Multiple arousals were seen as well (AI of 19 events/h at sea level vs. 29 events/h at 5,000 m). Subjects with periodic breathing have more arousals, however, the number of arousals that occurred in association with periodic breathing was typically only half the rate of the AHI. A good proportion



of the periodic breathing central apneas resolved in the absence of arousal. The spontaneous arousals were not affected by the increase in altitude [46]. The poor subjective quality of sleep may be attributed to either the multiple arousals associated with the termination of apneas and onset of hypercapnea or to changes in sleep stage distribution (e.g., increase stage 1 sleep) [47].

Following acute ascent to high altitude, sleep quality tends to improve with acclimatization. Undertaking a slow ascent and slow rise should be seen as the best measure to improve sleep at high altitude. However, some medications are available for the treatment of this condition.

### **Carbonic Anhydrase Inhibitors: Acetazolamide**

Administration of acetazolamide, a carbonic anhydrase inhibitor, is effective for treating AMS given both prophylactically and symptomatically. Acetazolamide inhibits carbonic anhydrase in the kidneys and lungs, promoting a slight metabolic acidosis. This effect counters the hypocapnic alkalosis produced by hyperventilation. As a result, AMS symptoms, including sleep disturbance, are reduced and the acclimatization process is hastened [48]. Nicholson et al. administered 500 mg daily of acetazolamide vs. placebo to six climbers during an expedition to the Himalayas. Acetazolamide increased stage 2 sleep and reduced wakefulness [49]. Fischer et al. found a slight decrease of stage 1 sleep, and increases in stage 4 and REM sleep on the first night at high altitude after administration of acetazolamide 250 mg twice daily for a couple of nights vs. placebo. Acetazolamide also improved oxygenation, decreased AHI and desaturation index [50]. These studies did not measure subjective sleep quality after acetazolamide. Other studies have demonstrated improvement on AMS scores (calculated through a point system of symptoms which included headache, loss of appetite, feeling sick, severe inappropriate weakness, dizziness, depression, irritability, drowsiness, cough, and shortness of breath); insomnia was not included as one of the symptoms after using acetazolamide [51]. The maximum dose is 5 mg/kg/day, taken in two or three doses. However 125 mg a day, taken 2 or 3 times or once at bedtime, may be adequate [48].

### **Benzodiazepines**

Temazepam has been studied as a treatment for insomnia at high altitude. Nicholson studied the sleep and respiration of six climbers during an expedition to the Himalayas. The subjects were assigned to age-matched pairs and were randomly allocated acetazolamide (500 mg daily) or placebo, and for two nights during the stay at high altitude (over 4,000 m) sleep was recorded one night with temazepam 10 mg and one night with matching placebo. Sleep was markedly disturbed in all subjects above 4,000 m. Temazepam shortened the mean sleep onset latency of the whole group from 33.8 to 22 min and increased the amount of REM sleep from 41.4 to 64.2 min. In the subjects not taking acetazolamide, temazepam increased stage 2

from 125.3 to 167.3 min and in the subjects taking acetazolamide, temazepam in combination shortened sleep onset latency from 41.1 to 17 min and increased sleep efficiency from 73 to 88%. The subjects reported that they slept better at high altitude with temazepam than with placebo. For the group, the number of respiratory disturbances was greater at high altitude than at sea level, but it was not possible to establish any differences between those using acetazolamide or placebo, or between those using the placebo and temazepam at high altitude [49]. Thus, hypnotics may improve sleep at high altitude, even without affecting respiratory variables.

Nickol et al. [52] examined the efficacy and safety of temazepam on nocturnal oxygenation and next-day performance at high altitude. Thirty-three subjects took 10 mg of temazepam and placebo in random order on two successive nights soon after arrival at 5,000 m. Compared with placebo, temazepam resulted in a reduction in periodic breathing, at the expense of a small but significant decrease in mean nocturnal oxygen saturation from 78 to 76%. There was no change in sleep latency or restlessness measured by actigraphy. Temazepam had no adverse effect on next-day reaction time, maintenance of wakefulness, cognition or AMS scores. Following temazepam compared with placebo, more subjects reported dropping off to sleep quicker than usual and sleeping better although these differences did not reach statistical significance.

It should be noted that doses as high as 30 mg of temazepam may be used for sleep at sea level and the above-mentioned studies were done with only a 10 mg dose. So, higher doses at high altitude have not been evaluated and cannot be recommended, due to its potential for reduced oxygen saturation [53]. Also, the drop in the oxygen saturation post-temazepam in healthy volunteers can be amplified in patients with underlying lung disease. Since no studies have been done in patients with pulmonary disease, this medication cannot be recommended in this population either. However, it is useful to have an alternative to the use of acetazolamide in patients with poor tolerance or with allergy to sulfa. Also it is important to know that cognitive function was not worsened with the dose mentioned above.

### **Non-benzodiazepine Benzodiazepine Receptor Agonists**

Studies evaluating the effect of these agents on symptoms of insomnia at high altitude have been done either in a simulator or in the field. Chamber and field studies done with zolpidem 10 mg and zaleplon 10 mg have demonstrated improvements in sleep onset latency and latency to S2 and SWS with both drugs; however the effects on SWS and TST were more significant with zolpidem. Neither zolpidem nor zaleplon influenced respiratory parameters at altitude. Compared to placebo, the AHI index or the mean or lowest  $\text{SaO}_2$  were not significantly affected by either drug. Cognitive performance and attention capacity were not reduced, and physical performance was not impaired, compared with a control night at sea level. AMS was also found to be reduced under both medications [54–56]. Reports of amnesia and somnambulism with the use of zolpidem, however, make this medication of potential risk especially in climbers in unsecured areas [57–60].

## Oral Steroids

Studies have shown amelioration of AMS symptoms with the use of dexamethasone. Dexamethasone 4 mg every 8 h starting 24 h before ascent or every 6 hours for six doses were utilized in two different studies. Also the use of prednisolone has been evaluated at high altitude. AMS symptoms were significantly lower compared to either acetazolamide or placebo. In two studies the assessment of AMS symptoms included reports about feeling refreshed/unrefreshed or insomnia. A prednisolone dose of 20 mg once a day was considered optimal [61, 62].

It is still unknown which mechanisms allow dexamethasone or prednisolone or other oral steroids, to improve AMS symptoms. It is postulated that steroids may act to improve the integrity of capillary membranes and induce cerebral vasoconstriction as it does with other types of vasogenic edema. Others postulate that the beneficial effects in AMS primarily are achieved by enhancing mood and relieving nausea [63]. More studies are required to determine the actual sleep pattern in high altitude while on treatment with oral steroids as well as in the quality of sleep and specifically in the improvement of insomnia.

## Other Medication Used to Treat Insomnia at High Altitude

Phenytoin has been studied in the potential treatment of AMS symptoms; however, it was found not to be effective [64]. Almitrine, a respiratory stimulant, was compared to acetazolamide and placebo in four healthy subjects at 4,400 m. Almitrine and acetazolamide both increased oxygen saturation during sleep; however, almitrine increased periodic breathing and acetazolamide was a superior agent at ameliorating periodic breathing [65]. Since periodic breathing is associated with arousals during sleep at high altitude, almitrine would not be an appropriate alternative to this type of insomnia. Theophylline is a respiratory stimulant through a central effect in ventilation. In a study by Kupper et al. [66], 20 healthy male volunteers were randomized to receive either 300 mg theophylline daily or placebo during ascent, and during a stay at 4,559 m altitude as well as 5 days prior to the expedition. Seventeen subjects completed the study. Theophylline, significantly reduced AMS symptoms, events of periodic breathing, and oxygen desaturations. No significant differences in sleep efficiency or sleep structure were present in the two groups. No adverse events associated to the drug were reported. Theophylline is well known for its narrow therapeutic window and multiple drug interactions. Due to the lack of clinical experience in AMS so far, it is not prudent to recommend this medication until further evaluations are done, especially with regard to safety. No studies have been done on the use of antihistamines for insomnia related to high altitude.

## Medications Used to Treat Insomnia

In a National Sleep Foundation Poll, 28% of self-defined insomniacs had used alcohol to help them fall asleep [67] and 23% used over-the-counter (OTC) medications for the same. Forty percent indicated using one or the other [5]. Drugs such as

**Table 14.1** Food and Drug Administration (FDA)-approved hypnotics

Type of drug	Dose (mg)	Half-life (hours)	Insomnia indications
Benzodiazepines <sup>a</sup>			
Triazolam (Halcion)	0.125, 0.25	2–6	
Temazepam (Restoril)	7.5, 15, 22.5, 30	8–20	
Estazolam (ProSom)	1, 2	10–24	
Flurazepam (Dalmane)	15, 30	48–120	
Quazepam (Doral)	7.5, 15	39–73	
Other benzodiazepine receptor agonists (BZRAs)			
Zaleplon (Sonata)	5, 10, 20	1	Sleep-onset insomnia
Zolpidem (Ambien)	5, 10	1.5–2.4	Sleep-onset insomnia
Zolpidem CR (Ambien CR)	6.25, 12.5	1.6–4.5	Sleep-onset and maintenance insomnia
Eszopiclone (Lunesta)	1, 2, 3	6	Sleep-onset and maintenance insomnia
Melatonin receptor agonist			
Ramelteon (Rozerem)	8	0.8–2	Sleep-onset insomnia
Tricyclic antidepressant/histamine-1 antagonist			
Doxepin (Silenor)	3, 6	10–50	Sleep-maintenance insomnia

<sup>a</sup>At the time these drugs were approved, there was no specific indication for onset or maintenance

alcohol, anesthetics, and narcotics can impair respiration due to the reduction of both hypoxic and hypercapnic ventilatory responses and their suppressive effect on maintenance of upper airway tone [16, 68].

### *Efficacy of Hypnotics*

The most commonly used and most investigated medications used for the treatment of insomnia are the benzodiazepine receptor agonists (BZRAs). These drugs function by binding to the benzodiazepine receptor at the GABA-A complex. These receptors are present in the membranes of neurons in the central nervous system (CNS) and peripheral nervous system (PNS). BZRAs include the traditional benzodiazepines, and a newer group of drugs called the non-benzodiazepines (i.e., zaleplon, zolpidem, zolpidem CR, zopiclone, and eszopiclone) [69].

The efficacy of Food and Drug Administration (FDA)-approved hypnotics is well documented. The medications listed in Table 14.1 have demonstrated efficacy for time to sleep onset, and depending on duration of action (i.e., dose and half life) reducing the duration of wake after sleep onset (WASO). All drugs have demonstrated efficacy using both PSG end points as well as patient-reported outcomes. Patient-reported outcomes are important as insomnia is a symptom-based diagnosis. Most clinical trials on insomnia have been done in primary insomnia, where no other disease states are present. This is important because it ensures that evaluations of hypnotic efficacy are not confounded by aspects of comorbid disease states or medications used to treat those diseases. However, as insomnia rarely presents as

primary, it is also critical to review the efficacy, benefits, and limitations (e.g., tolerance, abuse potential) of therapeutic agents for insomnia in the context of common comorbidities, particularly those that are encountered in pulmonary settings.

The most common insomnia comorbidity is depression. In a study of insomnia comorbid with depression, eszopiclone significantly reduced the time to sleep onset and reduced the amount of WASO [70]. More importantly it augmented the antidepressant response of fluoxetine. There are similar data with generalized anxiety disorder, rheumatoid arthritis, as well as menopause [71–73]. Unfortunately, to date, there are few studies with the aim of evaluating the efficacy of hypnotics in patients with insomnia comorbid with pulmonary disorders. To the extent these have been done, they have been done as safety studies. That is, they were performed and powered to determine if hypnotics worsen respiration during sleep.

COPD affects approximately 14 million people in the United States and is the fourth leading cause of mortality [74]. As mentioned previously, patients with COPD have difficulties with sleep, with slightly more than 50% of those patients complaining of difficulties initiating or maintaining sleep and 25% of them complaining of daytime sleepiness [26]. A multicenter study confirmed that 44% of elderly Italians with COPD had nocturnal awakenings, followed by morning tiredness (33%), early morning awakenings (30%), and difficulty falling asleep (26%) [75].

Benzodiazepines have been studied in patients with COPD. Cohn et al. [76] evaluated the effect of estazolam 2 mg vs. flurazepam 30 mg vs. placebo on the cardiopulmonary function of 29 patients with mild to moderate COPD. Criteria for entry included  $FEV_1$  ranged from 50 to 75%, end expiratory  $CO_2$  was  $\leq 45$  mmHg, and oxygen saturation on room air  $\geq 85\%$ . Although no difference on the ventilatory responses to  $CO_2$  were found, flurazepam decreased oxygen saturation and inspiratory time and increased respiratory frequency. In another study, Beaupre et al. evaluated the effect of therapeutically equivalent doses of diazepam (10 mg) and zopiclone (7.5 mg) compared to placebo on the respiratory center output of moderate to severe COPD patients (average  $FEV_1$  1 L). Diazepam produced a significant drop in the output of the respiratory centers compared to placebo following  $CO_2$  rebreathing. Zopiclone did not have any effect but produced an increase in respiratory frequency. There was no difference between the two active treatments [77]. Another study evaluated the effect of sublingual lorazepam 1.5–2 mg on the respiratory muscles of patients with severe COPD ( $FEV_1$  0.91 L). That study showed a drop in ventilation, reduction of the respiratory muscle strength, and resistance in patients with stable severe COPD [78]. These studies suggest the need for caution with these agents due to the potential for depression of the central respiratory drive in patients with COPD and worsening hypoxemia with these agents. To our knowledge, no efficacy studies with these agents in patients with COPD have been published.

Studies with short-acting non-benzodiazepine BZRAs such as zolpidem and zaleplon, have shown no significant effects on respiration in patients with mild to moderate COPD. In a study comparing zaleplon 10 mg, zolpidem 10 mg, and placebo, there was no effect on the mean overnight  $SAO_2$  or the percentage of the night with saturation less than 90% [79]. Girault et al. assessed the effects of repeated 10 mg oral doses of zolpidem compared to placebo on diurnal and nocturnal respira-

tory function, as well as on diurnal vigilance and physical performance in ten COPD patients with disordered sleep. Average  $FEV_1$  was 0.84 L. No impairment in nocturnal respiratory and sleep architecture parameters were noticed, nor on diurnal pulmonary function tests, central control of breathing, and physical evaluation [80]. The majority of studies so far have been done in patients with mild to moderate COPD. Until more data are available on the safety and efficacy of other BZRAs in patients with severe COPD, these agents cannot routinely be recommended. However, in patients with mild to moderate COPD with no awake hypercapnea, these agents can be useful [79].

Studies with Ramelteon, a melatonin receptor agonist, have been done in patients with mild, moderate, and severe COPD and it has been found to significantly increase TST and sleep efficiency without affecting oxyhemoglobin saturation, which can be explained through its completely different mechanism of action compared to the BZRAs [81–83]. Please refer to the section “Efficacy of Hypnotics” for more extensive information on this hypnotic agent. To the knowledge of the author, no studies on the use of doxepin in COPD patients have been published.

A prevalence of comorbid insomnia of 39–55% have been reported in patients with OSA [84]. A retrospective study of 231 patients with sleep disordered breathing (SDB) or upper airway resistance syndrome (UARS) showed a prevalence of insomnia symptoms slightly over 50% (116/231). The group was divided into two groups, the SDB plus insomnia (SDB+) and the SDB without insomnia symptoms (SDB–). After comparing the two groups there was a significant difference in the frequency of insomnia-related complaints such as sleep onset latency longer than 30 min (51% in SDB+ vs. 3% in SDB–), and difficulty returning to sleep once awake (59% in SDB+ vs. 10% in SDB–). It was also found that compared with patients with OSA alone, patients with both insomnia and OSA showed significantly longer SOL (17 vs. 65 min), shorter TST (5.6 vs. 7.2 h), and lower sleep efficiency (75% vs. 92%) by PSG [85]. In a prospective study of 105 patients referred for evaluation of suspected OSA, 102 of those patients were diagnosed with OSA and 39% of them met study criteria for insomnia. OSA severity was correlated with insomnia-symptom severity score [86].

Pre-existing insomnia could be one of the factors that can affect compliance with nasal CPAP; due to the sleep difficulties the CPAP mask can induce, including frequent awakenings and inability to initiate or return to sleep with the mask in place. In a retrospective chart review of 232 OSA patients treated with CPAP, 37% of them reported at least one frequent insomnia complaint with 23.7% reporting difficulty maintaining sleep, 20.6% reporting early morning awakening and 16.6% reporting difficulty initiating sleep. Sleep maintenance insomnia showed a statistically significant negative relationship with average nightly minutes of CPAP use as well as adherence status [87]. Since one of the predictors of chronic use of CPAP is early adherence to CPAP [88], it is possible that early diagnosis of insomnia and its treatment could help compliance with CPAP.

Insomnia coexists with anxiety and depression, and both pathologies may influence CPAP compliance. Patients with anxiety may be affected by claustrophobia, which has been associated with poor CPAP compliance as well [89]. Benzodiazepines

are commonly used for the treatment of insomnia; however, a high level of caution is recommended when these medications are considered in patients with OSA. Studies using benzodiazepines have shown their detrimental effect on ventilatory control, respiratory muscle function, and apnea events. A study comparing 30 mg of flurazepam vs. placebo showed an increased of apnea episodes (9.95 vs. 5.35) and longer duration of apneas (3.44 vs. 1.72 min) in the flurazepam group [90]. In another study using triazolam 0.25 mg, patients with severe OSA showed an increased arousal threshold which resulted in prolongation of event duration and increased desaturation [91]. However, in another study using Temazepam 15–30 mg in elderly subjects with mild sleep apnea and insomnia, there was no increase in the respiratory disturbance index (RDI) as compared with the non-drug group [92]. The effect could have been different if patients with moderate or severe OSA were included. At this point, the regular use of benzodiazepines for insomnia in OSA patients cannot be broadly recommended since it can produce worsening of the severity of the underlying disease as well as hypoxemic events.

Non-benzodiazepine BZRAs have been studied in OSA patients as well. In a study of 16 patients with severe OSA treated with CPAP, the use of zolpidem 10 mg did not affect the AHI, oxygen desaturation index or the lowest oxygen saturation [93]. In another study, zolpidem 10 mg was administered to ten healthy non-obese snorers. Zolpidem increased TST, sleep efficiency, and the percentage of stage 2 sleep. Zolpidem did not affect the TST spent snoring nor desaturation parameters. The RDI was modestly increased by zolpidem from an average of 1.5–3 events/h, however this is still under 5 which is within normal limits [94]. A pilot study on patients with mild to moderate OSA ( $\text{AHI} \geq 10$  and  $\leq 40$ ) received eszopiclone 3 mg vs. placebo. The night of the study, patients were not allowed to use CPAP. There was no worsening on the AHI while on eszopiclone, and there was improvement in sleep maintenance and sleep efficiency [95]. The use of eszopiclone 3 mg has also been shown to improve the quality of diagnostic PSG and CPAP titration. Eszopiclone reduced sleep latency, improved sleep efficiency, reduced WASO, and prolonged sleep time [96]. It has also been demonstrated that the use of 3 mg of eszopiclone for 14 days at the onset of CPAP therapy improves long-term CPAP adherence compared to placebo in adults with OSA. The eszopiclone group used CPAP for 21% more nights, 1.3 more hours per night for all nights, and 1.1 more hours per nights when CPAP was used. The hazard ratio for discontinuation of CPAP was 1.9 times higher in the placebo group [96]. The effect of these hypnotics in patients with severe sleep apnea determined by either AHI or associated severe desaturation, has yet to be determined. However, the use of these hypnotics in association with CPAP looks to be safe and may improve adherence to CPAP therapy. We do not yet know what specific group of patients will benefit the most from this combination. Thus far, the use of zolpidem or eszopiclone in patients with OSA with or without insomnia, have improved CPAP compliance. However, to our knowledge, studies to assess CPAP compliance improvement on patients with insomnia and OSA have not been published.

In a recent study, ramelteon, a melatonin receptor agonist, was used in older adults with insomnia and sleep apnea who started treatment with auto-titrating positive airway pressure (APAP) therapy for sleep apnea. Ramelteon 8 mg for 4



weeks was compared to placebo. Ramelteon was effective at improving objective but not subjective sleep onset latency in this group of patients and it did not improve APAP adherence [97]. Further research is required with this medication especially in patients with sleep onset insomnia prior to further recommendations. Thus far, due to the mechanism of action of Ramelteon and through efficacy and safety studies done in patients with mild to severe COPD, it has been shown not to affect AHI or to worsen hypoxemia [81–83].

## Safety of Medications Commonly Used in Insomnia

When traditional benzodiazepines were introduced approximately five decades ago as a treatment for insomnia, they represented a major advance in the therapy of this disorder. They are more effective and safer than drugs used previously, such as barbiturates. However, concern about side effects, tolerance, and dependence has been raised [98]. The major adverse effects of BZRAs include psychomotor and cognitive (anterograde amnesia) impairment, discontinuation effects (i.e., rebound insomnia), and risk of dependence. The incidence and severity of these side effects, particularly residual impairment upon awakening, are primarily determined by drug dosage and half-life which determine the duration of action of medications. Thus, the longer the half-life or the higher the dose, the greater the likelihood of residual effects. In terms of the amnesic effects, all BZRAs produce anterograde amnesia and this seems to be related to both binding specificity and sedative potency.

Tolerance to a drug is defined as the reduction of its effect with repeated administration of a constant dose, or the need to increase the dose to sustain a specific level of effect. Tolerance to the hypnotic effects of BZRAs does not develop in the vast majority of studies, at least for therapeutic doses and for the periods of time (3–6 months) that have been studied [99]. These consistent clinical trial findings are inconsistent with many clinicians view that tolerance to these medications does occur with chronic use. This causes clinicians to use the lowest possible dose. Thus, the loss of efficacy may really be a worsening of the insomnia or the comorbid disorder.

Dependence has been a concern with hypnotic medications. Epidemiologic data has shown that for 74% of users of hypnotics the longest period of daily use was less than 2 weeks [100]. 1% of individuals use them nightly on a chronic basis with rare dose escalation. It is unlikely that this pattern of use reflects dependence in the vast majority of patients, given the absence of dose escalation or non-therapeutic use of the medication [101–103]. Although there are reports of physical dependence at therapeutic doses in long-term daytime use of benzodiazepines for treating anxiety disorders, no such data has been found in insomnia patients. Daytime studies of the reinforcing effects of these drugs indicate that they have a low behavioral dependence liability [104].

However, it is important to recognize that individuals with a risk for abuse, will abuse BZRAs. Abuse of sedatives, particularly the benzodiazepines diazepam (anxiolytic) and flunitrazepam (hypnotic not approved in US), has been a particular problem



in populations of abuse such as methadone maintenance patients and intravenous drug abusers. On a population basis, the incidence of recreational abuse of sedatives/hypnotics and related drugs is relatively rare, but it is similar to the incidence of abuse of other illicit substances. The risk of abuse or problematic use of hypnotic drugs is significantly elevated among patients with histories of drug or alcohol abuse or dependence [105]. Based on this information, physicians are strongly discouraged from prescribing BZRA hypnotics to patients with a history of drug abuse.

More recently, the non-benzodiazepine BZRAs were developed and act predominantly at the  $\alpha 1$  subunit through the  $\alpha 3$  subunits. Studies with genetically modified mice have confirmed that receptors containing  $\alpha 1$  subunits play a particularly important role in mediating sedative activity as well as the amnestic effects of these compounds. It has been hypothesized that non-benzodiazepine BZRAs produce fewer adverse side effects on pulmonary function than do the benzodiazepines [106]. Drugs in this subclass include zolpidem, zolpidem CR, zopiclone, and its active racemate eszopiclone and zaleplon as listed in Table 14.1. While zolpidem and zaleplon are highly selective for the  $\alpha 1$  subunit, zopiclone and eszopiclone are less selective with comparable affinity for  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$ , and  $\alpha 5$  subunits [69, 107]. The non-benzodiazepine BZRAs have similar effects on sleep latency and maintenance as traditional benzodiazepines [69]. Differences in the relative efficacy for the BZRAs relate most importantly to dose and half-life, the primary determinants of duration of action. Overall, shorter acting hypnotics such as zaleplon ( $t_{1/2}=1$  h) and zolpidem ( $t_{1/2}=2-6$  h) are effective at improving sleep onset latency while higher doses or longer-acting compounds are also effective for maintaining sleep.

Several studies have been performed to test the safety of these medications on pulmonary and cognitive function. Ranlov and Nielsen compared the effects of equipotent, single intravenous doses of zopiclone (7.5 mg) and diazepam (10 mg) on ventilatory responses in ten healthy volunteers. Ventilatory parameters were measured before and after the injections during the early afternoon in the wake state. The intravenous administration of diazepam induced a significant reduction in the  $\text{CO}_2$  stimulated ventilatory responses. The total ventilation after 5 and 35 min of the zopiclone injection during the 4 min of  $\text{CO}_2$  rebreathing experiment was 3.35 and 3.01 L/m<sup>2</sup>/PCO<sub>2</sub>, respectively. The total ventilation of 5 and 35 min injection of diazepam was 2.83 and 2.55 L/m<sup>2</sup>/PCO<sub>2</sub> which was significantly lower. While on zopiclone and after the rebreathing method, the respiratory rate also increases from a baseline of 16.7 bpm to a range between 19.5 and 20.4 bpm over a period of 4 min during the rebreathing method. This effect was not seen after the injection of diazepam [108].

Cohn evaluated the effects of single oral doses of zolpidem 10 or 20 mg, codeine phosphate 60 mg, or placebo in wake normal volunteers. Ventilatory responses to  $\text{CO}_2$  and mouth occlusion pressure, measured 1 hour before and at 1 and 3 hours after each administered dose (approximate  $t_{\text{max}}$ ), were not significantly affected by either zolpidem each administered dose; however, codeine phosphate produced a small but significant respiratory suppressant effect at 3 hours. Non-significant changes in mean inspiratory flow were noted after zolpidem 10 mg. Two hours after administration of zolpidem 20 mg, mean inspiratory flow was significantly lower than after placebo, possibly related to some individuals falling asleep during data collection [109].

Berry et al. evaluated the effect of triazolam on the arousal response to airway occlusion during NREM sleep. Mask occlusion was performed 1–4 h after triazolam 25 mg or placebo ingestion, while the subjects breathed a mixture of air and oxygen adjusted to produce an arterial oxygen saturation of 98%. Time to arousal was significantly longer on triazolam nights ( $32 \pm 5.2$  vs.  $22.5 \pm 3.2$  s). The maximal airway suction pressure preceding arousal was also significantly higher on triazolam nights ( $26.5 \pm 2$  vs.  $20 \pm 1.2$  cm H<sub>2</sub>O). Conversely, the rate of increase in inspiratory effort (maximal pressure) during occlusion was not decreased by triazolam [110]. This arousal blunting effect of hypnotics is important to consider in patients with OSA where the termination of the obstructive event depends largely on arousal. More broadly, most physiological responses produced by internal stimuli (e.g. cough) require arousal, and blunting the arousal response may have negative consequences. However, blunting arousal response may help sleep by preventing arousal to external stimuli. In patients with comorbid medical conditions potential negative consequences need to be considered. In addition, there are the potential amnestic and cognitive effects that non-benzodiazepines BZRAs have, similar to benzodiazepines [111]. There are also reports of abnormal behaviors in sleep such as sleep eating, sleep walking, and anterograde amnesia associated with zolpidem use [112].

Ramelteon, a melatonin receptor agonist, is a hypnotic agent approved by the US FDA in 2005 for the treatment of insomnia characterized by difficulty falling asleep and it is not a controlled substance [113]. Three melatonin receptors, MT1, MT2, and MT3, have been identified with wide distribution throughout the body and brain. The sleep-promoting effect of ramelteon is mediated by MT1/MT2 receptors. Ramelteon has no affinity for the MT3 receptor which may mediate other functions including effects on the gastrointestinal system [69]. Ramelteon has no known affinity for the benzodiazepine or any other receptor at the GABA-A complex or receptors that bind neuropeptides, cytokines, serotonin, dopamine, noradrenaline, or opiates [113]. In clinical trials, ramelteon has produced significant reductions in latency to persistent sleep compared with placebo. Additionally, improvements in TST were sometimes observed. The most common adverse events reported with ramelteon included headache (7%), dizziness (5%), somnolence (5%), fatigue (4%), and nausea (3%) [113].

Some physicians who prescribe sedative hypnotics are concerned about the possibility of dependence especially in patients with prior history of abuse. Johnson et al. evaluated the abuse potential of ramelteon in doses up to 160 mg. Compared with placebo and triazolam, ramelteon showed no significant effect on measures related to abuse [114].

No studies have been done so far to assess the effect of ramelteon on control of breathing. However, studies that assess the effect of ramelteon on respiration have been done in patients with mild to moderate COPD, moderate to severe COPD, and mild to moderate OSA. In those studies, there was no significant difference in the level of oxyhemoglobin saturation throughout the night and no increase in the AHI between the ramelteon and the placebo nights. In patients with moderate to severe COPD, ramelteon has been found to significantly increase TST and sleep efficiency [81–83]. These findings have expanded our options for treatment of insomnia in patients with prior history of substance abuse and lung disease.

## Sedating Antidepressants

As the highest comorbidity with insomnia is depression, it is not surprising that the most common medications utilized in the United States for off label treatment of insomnia are the sedating antidepressants. Leger and Poursain [115] found that when patients in United States were prescribed a medication for insomnia, 22% of the time they were prescribed sedating antidepressants. In 2002, trazodone was the most prescribed drug for insomnia, with amitriptyline and mirtazapine ranked as third and fourth, respectively [104]. However, there is little evidence to support their use as a treatment for insomnia without depression [116]. Importantly, while we know the range of doses that are effective in depression, and the side effects associated with those doses, no one knows the doses that are effective for insomnia and the side effects of those doses. Several antidepressants are commonly used for the treatment of insomnia, even in patients without concomitant anxiety/depressive disorders and despite the lack of evidence regarding their efficacy or safety. Among the antidepressants those which are histamine antagonists, and 5HT<sub>2A</sub> or 5HT<sub>2C</sub> antagonists are the ones most commonly used.

Doxepin was approved in 2010 by the FDA for the treatment of insomnia characterized by difficulty in maintaining sleep. Doxepin is a tricyclic antidepressant (TCA) with relatively selective antagonism of the histamine 1 (H<sub>1</sub>) receptor at the doses approved for insomnia (i.e., 3 and 6 mg). H<sub>1</sub> antihistamines have sedative properties. At antidepressant doses (75 mg and higher), Doxepin inhibits postsynaptic H<sub>2</sub>, serotonin 5HT<sub>2</sub>, adrenergic  $\alpha$  1, and muscarinic receptors, but has little effect on postsynaptic dopaminergic D<sub>2</sub> and adrenergic  $\alpha$  2 receptors [117]. However, as the dose of doxepin lowers, it is a highly selective H<sub>1</sub>-receptor antagonist, four times more potent than amitriptyline and 800 times more potent than diphenhydramine [118]. Doxepin has been studied at doses of 1, 3, and 6 mg in young and elderly patients with transient and chronic insomnia [119–122]. In those studies, doxepin showed significant improvement in WASO, TST, and overall sleep efficiency (SE), even at the 1 mg dose. With higher doses, sleep efficiency showed further improvement. Significant improvement in sleep efficiency at all doses in the final third of the night was also demonstrated which emphasizes its therapeutic potential in patients with sleep maintenance insomnia, a common complaint in patients with underlying obstructive lung disease [26]. Also, due to its mechanism of action, it is unlikely that it will affect pulmonary function or ventilator parameters during sleep; however, those studies have yet to be done. At all three doses doxepin did not show statistical differences in next-day residual sedation and sleep architecture was preserved relative to placebo. The most common treatment emergent adverse events that occurred with doxepin relative to placebo were somnolence/sedation, upper respiratory tract infection/nasopharyngitis, gastrointestinal effects (gastroenteritis, nausea), and hypertension [117]. There was no evidence of physical dependence or worsening insomnia after doxepin discontinuation.

Trazodone has been utilized frequently for the treatment of insomnia, even though it is not an FDA-approved hypnotic. Trazodone is a phenylpiperazine-sedating

antidepressant. It is a weak but specific inhibitor of the serotonin reuptake transporter with minimal affinity for NE or dopamine reuptake. Trazodone also inhibits different serotonin receptors. The sedating mechanism is not well elucidated but it is presumed to be related to its antihistaminergic or antiserotonergic activity similar to other sedating antidepressants such as TCAs [116, 123]. As an antidepressant, trazodone has the advantages of low cost, no restrictions on long-term prescription, and low abuse potential. However, side effects of trazodone include orthostatic hypotension, blurred vision, nausea, dry mouth, constipation, drowsiness, headaches, and has been associated with cardiac arrhythmias [116, 124]. The question remains at what doses does trazodone improve insomnia, and are these side effects present at those doses. There are virtually no studies to assess the effect of trazodone in respiratory function or in patients with pulmonary disorders. Due to its mechanism of action, problems with ventilation are not expected necessarily. However, that will need to be assessed prior to recommending this medication based on the potential for significant side effects. Given the common side effects of trazodone and the potential for tolerance to develop with just 2 weeks of treatment, it is unclear if the risk/benefit ratio warrants trazodone's use in non-depressed patients with insomnia [125].

## Cognitive-Behavioral Therapy of Insomnia

Psychological and behavioral therapies for insomnia include sleep restriction, stimulus-control therapy, relaxation training, cognitive strategies, sleep hygiene education, and combined CBT. The main objective of CBT is to alter those factors that perpetuate or exacerbate sleep disturbances such as poor sleep habits, irregular sleep-wake schedules, hyperarousal, inadequate sleep hygiene, and misconceptions about sleep and the consequences of insomnia. CBT is mainly indicated in patients with persistent insomnia, either primary or comorbid. There are no actual contraindications to CBT. However, one of its components, sleep restriction, can produce sleepiness and patients should be cautioned about that possibility. Studies have shown that CBT is effective for treating insomnia associated with chronic pain, fibromyalgia, cancer, and various medical conditions in older adults [126]. CBT has also been tested in patients with COPD and OSA with comorbid insomnia. After CBT, these patients showed improvement in several self-reported measures of sleep along with improvement on reports of daytime functioning [127, 128].

## Other Medications

Other medications used in the treatment of insomnia including antipsychotics, quetiapine, and olanzapine have been used in the treatment of insomnia in patients without psychiatric comorbidities. Their sleep effect is thought to be related to their antihistaminic activity. There is no information on their efficacy and safety when used as hypnotics in primary insomnia [98]. OTC sleep medications most commonly

contain diphenhydramine (25 mg), a well-known H1 antihistamine as the active ingredient. Their hypnotic effect is variable and can result in daytime sleepiness, cognitive impairment, and anticholinergic effects that persist a day after ingestion, potentially affecting driving performance [129]. Importantly, tolerance develops rapidly (~4–5 days) to the sedative effects of diphenhydramine [130]. BZD anxiolytics have also been used for the treatment of insomnia. These include clonazepam, alprazolam, and lorazepam. Their half-lives are longer than the hypnotics in the same class. There are no studies done to assess safety or efficacy when BZD anxiolytics are used as hypnotics [98]. Very few studies have been done to assess the efficacy and safety of the use of herbal agents to treat insomnia. Some studies have been done with valerian showing no improvement on self-reported or PSG sleep relative to placebo. St John's Wort is another herbal product promoted for the treatment of different conditions, such as depression, anxiety, and sleep disturbances. No studies have been done to assess its efficacy or safety on the treatment of insomnia [131].

## Summary of Keypoints

- The majority of people with insomnia have comorbid medical disorders, such as conditions causing hypoxemia and dyspnea, gastroesophageal reflux disease, pain conditions, and neurodegenerative diseases. Treatment can be challenging, especially if multiple comorbidities are present.
- The curriculum of medical education lacks attention to sleep disorders and physicians in general often fail to ask patients about their sleep.
- Treatment for insomnia includes CBT and pharmacological therapy.
- Patients with a variety of pulmonary disorders often suffer from sleep disturbance. However, further differentiation between sleep initiation and sleep maintenance insomnia is lacking. This differentiation should be made clear in order to effectively guide pharmacological therapy.
- Studies to assess safety and efficacy of benzodiazepines and non-benzodiazepine BZRAs have been conducted especially in patients with COPD but not in other pulmonary disorders such as ILD and restrictive thoracic cage disorders (RTCD).
- Benzodiazepines have shown to produce a drop in ventilation, reduction of the respiratory muscle strength, and increases upper airway resistance in patients with stable severe COPD.
- Studies with short-acting non-benzodiazepine BZRAs such as zolpidem and zaleplon, have shown no significant effects on respiration in patients with mild to moderate COPD. Until more data are available in patients with severe COPD, these agents cannot routinely be recommended. However, in patients with mild to moderate COPD with no awake hypercapnea, these agents can be useful.
- Ramelteon, a new FDA-approved hypnotic for initiation insomnia has been evaluated among patients with mild to severe COPD and has been found to be safe and efficacious for the treatment of insomnia.

- New FDA-approved hypnotics such as ramelteon and doxepin, due to their lack of broad CNS suppression, might be safe in patients with respiratory disorders; however, safety and efficacy studies are still needed.
- Patients with OSA show sleep onset and sleep maintenance insomnia. The use of benzodiazepines increases the frequency of apneas and prolongs the duration of apnea events. The use of non-benzodiazepine BZRAs have not worsened the AHI or duration of apneas. Also some non-benzodiazepine BZRAs increase compliance with CPAP. But this needs to be studied in patients with concomitant insomnia and OSA.
- CBT has been tested in patients with COPD and OSA with comorbid insomnia. After CBT, these patients showed improvement in several self-reported measures of sleep along with improvement in daytime functioning. Further studies on the safety and efficacy of CBT in patients with other pulmonary disorders and comorbid insomnia are needed.

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# Chapter 15

## Circadian Disorders

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**Keywords** Circadian • Light • Melatonin • Sleep phase • Jet lag • Shift work

### Circadian Biology

Circadian rhythms are near-24 h cycles that exist in all living organisms. Examples in humans include the core body temperature rhythm, hormonal secretion rhythms, and the sleep/wake cycle. Lung function and heart rate also demonstrate circadian rhythmicity in that they cycle daily even in the absence of external influence [1, 2]. The master clock which regulates and coordinates the body's many rhythms is the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [3]. The molecular machinery in the SCN neurons that generates and perpetuates the circadian rhythm consists of clock gene products which autoregulate their own expression through a complex system of transcriptional, translational, and post-translational processes [4]. These clock genes are also expressed in various other tissues in the body, e.g., heart [5], liver [6], lungs [7], and kidney [8], generating circadian rhythmicity to numerous physiological parameters. In fact, about 10% of all genes in the heart and liver have a circadian pattern of expression, underscoring the importance of circadian regulation in normal physiology.

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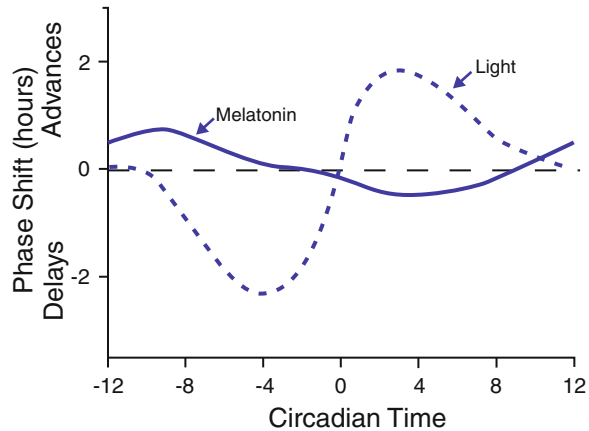
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**Fig. 15.1** Phase-response curve to light and melatonin. Circadian time 0 = time of temperature nadir. Note the magnitude of phase shift to light as compared to melatonin. Adapted with permission from Minors et al. [34] and Burgess et al. [16]



The most evident human circadian rhythm is the sleep/wake cycle. The prevailing model of human sleep regulation describes the interaction between the circadian system and the homeostatic sleep process such that the circadian clock promotes and maintains wakefulness during the day while the homeostatic sleep process opposes the circadian system by monotonically increasing sleep tendency throughout the waking period until sleep is achieved in the evening [9, 10]. There is actually a biphasic circadian rhythm to sleep tendency, with a dip in alertness approximately 6–8 h after waking, followed by an increase in alertness through the early evening hours [11]. Sleep homeostasis is gradually dissipated throughout the sleep period. The sleep/wake cycle is thus the result of complex interaction between two systems.

While the sleep/wake cycle may be an outward display of the circadian rhythm, classical phase markers of the endogenous circadian rhythm that are commonly used in research include melatonin rhythm and body temperature rhythm. Both rhythms have distinct phase relationships with the sleep/wake cycle such that the dim light melatonin onset (DLMO – time at which melatonin level starts to rise) is about 2–2.5 h before sleep onset and core body temperature nadir is about 2 h before sleep offset [12] in normal phase individuals. As expected, when circadian rhythm is phase shifted, the endogenous melatonin and body temperature rhythms will shift accordingly.

The free-running period (the frequency of oscillation) of the human endogenous circadian clock is usually slightly longer than 24 h; therefore, the SCN must synchronize or entrain itself to the 24 h environment daily in order for sleep/wake to occur at the same time every day [13]. This entrainment is best accomplished by light exposure, physical activity, and melatonin from the pineal gland. Light input to the SCN, through the ganglion cells of the retina, is the most potent entraining agent and the effect of light on the circadian system is dependent on the timing of exposure. Light exposure during the first half of the night will delay the timing of the circadian rhythm, whereas early morning light exposure will advance the rhythm [14, 15]. Melatonin secretion from the pineal gland occurs during the night

via input from the SCN and exogenous melatonin administration can also influence the circadian system. Opposite to the effect of light exposure, melatonin given at night will advance the timing of the circadian rhythm and early morning dosing will delay the rhythm [16] (Fig. 15.1). Light and melatonin are often used in the treatment of circadian rhythm sleep disorders (CRSD).

## Circadian Rhythm Sleep Disorders

CRSD result from either alterations of the intrinsic circadian clock (delayed sleep phase disorder (DSPD), advanced sleep phase disorder (ASPD), free-running type, and irregular sleep–wake rhythm) or misalignment between the intrinsic circadian rhythm and the external 24-h environment (shift work and jet lag) which leads to symptoms of insomnia or excessive daytime sleepiness. In addition, *The International Classification of Sleep Disorders* states that the sleep disturbance in a CRSD must be associated with social, occupation, or other functional impairments [17]. Besides physiological and environmental factors, maladaptive behaviors can influence the clinical course of CRSD.

### *Delayed Sleep Phase Disorder*

DSPD is characterized by chronic inability to fall asleep and wake up at desired times. Typically the patient cannot fall asleep until 2–6 a.m., and when not constrained by social or work schedule, will wake up between 10 a.m. and 1 p.m. [18]. Because most patients attempt to conform to conventional work and school schedules, however, they complain of insomnia and excessive daytime sleepiness. When not required to maintain a strict schedule (i.e., on weekends and holidays), patients report a normal sleep period without sleep complaints. DSPD is one of the more common CRSD, affecting 0.17% of general population and greater than 7% of adolescents [19, 20].

Although the exact pathophysiology is unknown, proposed mechanisms include a prolonged circadian period, hypersensitivity to evening light which delays the circadian clock, and altered homeostatic regulation of sleep to prevent phase advancement [21, 22]. Genetic studies have suggested an autosomal dominant mode of inheritance with incomplete penetrance, and genetic polymorphism of several clock genes have shown associations with DSPD [23]. *Per3*, *Arylalkylamine N-acetyltransferase*, and *Clock* have all been implicated, but interestingly, both alleles of the *Per3* length polymorphism have shown association with DSPD [24–26]. Specifically, the four-repeat allele of the polymorphism, and not the five-repeat allele, was associated with DSPD in a European cohort while only the five-repeat allele of the polymorphism was associated with DSPD in a South American cohort [24, 27].

## Diagnosis of Delayed Sleep Phase Disorder

Most of the patients who present with DSPD are adolescents or young adults, although DSPD has also been described in older adults [28]. Diagnosis of DSPD can usually be made from a detailed sleep history along with sleep diary and/or actigraphy for at least 7 days in order to capture weekend or non-working days to ensure patients exhibit a delayed sleep and wake pattern. Actigraphy utilizes a wrist-worn motion detector to monitor sleep and wake pattern for long periods (usually days to weeks). Polysomnography is not necessary for the diagnosis of DSPD unless there is concern for concomitant sleep apnea or periodic limb movement disorders [29]. When performed during the patient's desired sleep and wake period, polysomnography should demonstrate normal sleep architecture and sleep stage distribution; however, sleep onset latency may be prolonged [30].

Diagnosis of DSPD should only be made after exclusion of other causes of insomnia and daytime sleepiness. DSPD should also be differentiated from late sleep and wake times which do not lead to daytime functional impairments. Both primary and comorbid insomnias can have features of sleep-onset insomnia, but a patient with DSPD will not have insomnia when allowed to sleep at desired time. Daytime sleepiness may also be caused by other sleep disorders (e.g., sleep apnea, narcolepsy, etc.) medical, neurological, and psychiatric disorders, as well as medication and substance abuse. The circadian nature of DSPD should allow differentiation from other similar complaints. DSPD is strongly associated with mood disorders, including depression and anxiety, and psychiatric screening should be considered for patients [31, 32].

## Treatment of Delayed Sleep Phase Disorder

Treatment of DSPD is aimed at realigning the endogenous circadian rhythm, and hence the sleep/wake cycle, with the desired social and work schedule. Options for advancing the timing of the sleep/wake cycle include chronotherapy, bright light therapy, and melatonin administration. Chronotherapy is a method by which an individual is phase delayed 3 h every 2 days until the desired sleep time is achieved [33]. Although an effective therapy, chronotherapy is disruptive to the daily routine and requires strict adherence to control of light exposure and sleep/wake times. Chronotherapy was initially implemented on an in-patient basis, but has since been successfully performed at home with well-structured, patient driven protocol. The major limitations of chronotherapy are the duration of therapy and the restrictions it places on social and professional responsibilities. While the therapy lacks any controlled studies, it nevertheless is a viable treatment option for DSPD [29].

Bright light therapy is effective at altering the phase of the sleep/wake cycle [14]. The influence of light on the human circadian rhythm depends on the timing and intensity of light exposure and is described by the phase-response curve of light [14, 34]. Light given before the body's temperature nadir will phase delay the circadian rhythm, while light given after temperature nadir will cause a phase advance. In general, light given closer to temperature nadir will cause a more dramatic phase shift.



**Table 15.1** Overview of diagnosis and treatment of circadian rhythm sleep disorders (CRSD)

Circadian disorder	Main diagnostic criteria	Treatment
Delayed sleep phase disorder	Delay in sleep period relative to desired sleep and wake times, causing insomnia and difficulty waking up	Sleep hygiene Bright light therapy: 2,000–2,500 lx for 2–3 h prior to or at rise time Melatonin (1–3 mg): 5–7 h before sleep time
Advanced sleep phase disorder	Advance in sleep period relative to desired sleep and wake times, causing difficulty staying awake in the evening and inability to stay asleep in the morning	Bright light therapy: 2,000–2,500 lx for 1–2 h in evening (approximately 7–9 p.m.) Melatonin (theoretical benefit): 1–3 mg after rise time
Shift work disorder	Excessive sleepiness and reduced performance during work shifts that overlap with the usual sleep period. Insomnia symptoms and shortened or fragmented sleep, especially during the day	Sleep hygiene Bright light therapy: 2,500–9,500 lx for 2 h during work shift Melatonin: 1–3 mg before sleep time Caffeine Scheduled naps: 1–2 h nap prior to work shift. Short 10–20 min naps during work shift Modafinil 200 mg or armodafinil 150 mg: take 1 h prior to work shift
Jet lag	Eastward travel: Difficulty falling asleep in the evening. Excessive sleepiness and grogginess in the morning Westward travel: Excessive sleepiness in the afternoon or early evening. Early morning or middle of the night awakening	Sleep hygiene Eastward travel: avoid evening light Bright light in the mornings Melatonin 1–5 mg at local bedtime Westward travel: avoid morning light Bright light in the evenings

The American Academy of Sleep Medicine recommends morning light therapy for the treatment of DSPD but the exact timing, duration, and intensity of light have not been determined [29]. Based on two controlled trials, 2,000–2,500 lx of light for 2–3 h prior to or at rise time is recommended. Caution should be taken to not start light therapy before temperature nadir to avoid further phase delay. Avoidance of bright light in the evening is also advised.

The mainstay of pharmacotherapy for DSPD is melatonin. Similar to light therapy, exogenous melatonin can shift the circadian rhythm based on the phase-response curve of melatonin. Maximum phase advance is seen when melatonin is administered 3–5 h before DLMO in normal phase individuals [16, 35]. Studies using melatonin for DSPD patients have used different doses and have shown different optimal times of administration. One study found that 0.3 or 3 mg of melatonin caused the greatest sleep phase advancement approximately 6 h before sleep onset in DSPD patients [36]. Hypnotics and stimulants have not been well studied for treating the symptoms of DSPD and are currently not indicated for the disorder (Table 15.1) [29].



Successful management of DSPD often requires a multimodal approach. In addition to bright light and melatonin, patients should be instructed on proper sleep hygiene. Discussion with the patient on treatment compliance is important for difficult therapeutic options such as chronotherapy and bright light therapy. It is also essential to identify and treat comorbid psychiatric disorders as well as minimize maladaptive behaviors [37].

### ***Advanced Sleep Phase Disorder***

ASPD is characterized by sleep/wake times that are several hours earlier than desired or conventional times. Affected individuals have habitual sleep time between 6 and 9 p.m., and wake time between 2 and 5 a.m., and staying up past 9 p.m. is often very difficult. The prevalence of ASPD is much lower than that of DSPD, estimated at approximately 1% of middle-aged adults [38]. Underreporting may contribute to the lower prevalence of ASPD as an early sleep pattern tends to lead to less work and social conflicts compared to a late sleep pattern. Although ASPD is widely believed to be more common with aging, conclusive data are lacking to support this belief [39]. However, a survey of adults 40–65 years of age did find that “advance-related” complaints were twice as common as “delay-related” complaints (7.4% vs. 3.1%) [28].

Similar to DSPD, the etiology of ASPD is not well defined and could be multifactorial. Potential mechanisms include a shortened circadian period, as found in one patient from a family of ASPD subjects, and retinal hypersensitivity to light in the morning, which may maintain phase advancement of the circadian rhythm [40, 41]. Genetic analysis of ASPD families has revealed an autosomal dominant inheritance pattern and a missense mutation of the clock gene *Per2* [42, 43]. Highlighting the genetic heterogeneity of the disorder, other families with ASPD did not have the same mutation; instead, a mutation in the *CK1 $\delta$*  gene was recently found in a separate family with ASPD [44].

### **Diagnosis of Advanced Sleep Phase Disorder**

Chronic complaints of early evening sleepiness and early morning awakening/insomnia are always present patients with ASPD. When trying to conform to a conventional sleep schedule due to work or social obligations, patients become progressively sleep deprived as bedtime becomes delayed and they continue to wake up earlier than desired. As a result, patients often complain of excessive daytime sleepiness.

Sleep diary and/or wrist actigraphy recording for at least 7 consecutive days is recommended to demonstrate stably advanced sleep and wake times, especially on weekend or non-working days. Polysomnography performed at the patient’s desired sleep time should show normal sleep architecture and total sleep time. It can also be

useful to exclude other sleep disorders that can lead to daytime hypersomnia [17]. The prominence of early morning awakening as a symptom in ASPD should prompt an evaluation for comorbid depression.

### **Treatment of Advanced Sleep Phase Disorder**

Bright light therapy and chronotherapy have been used to delay sleep/wake times in ASPD with success. Evening bright light has been shown to delay sleep onset and morning awakening, increase total sleep time, and reduce wake after sleep onset. As expected, body temperature and melatonin rhythms are also delayed with light [45, 46]. The duration and timing of light treatment and light intensity have not been clearly defined [29].

Chronotherapy was described to successfully treat ASPD in one case report. The patient's usual sleep time of 6:30 p.m. was slowly advanced to 11 p.m. over 2 weeks by advancing his sleep time 3 h every 2 days. The patient was able to maintain his new sleep time of 11 p.m. after he left the hospital for 5 months [47]. Chronotherapy has not been studied further, however, and practicality may limit its clinical use.

While melatonin administration has been shown to phase delay circadian rhythms, no studies have examined its efficacy in ASPD [48]. Melatonin administered in the morning should phase delay the sleep/wake rhythm and would be ideal for patients with ASPD. Clinicians should be aware of its soporific effect and potential for morning drowsiness with administration. Given the limited treatment options for ASPD, however, melatonin is a potential therapeutic option that should achieve higher compliance rate than chronotherapy or bright light therapy.

### ***Free-Running Type***

When the endogenous circadian rhythm cannot be entrained by the light–dark cycle, the rhythm will free run. Since the human free-running circadian period is usually >24 h, the sleep–wake cycle gradually drifts each day. This is often observed in blinded individuals whose retinohypothalamic tract does not transmit light and dark signals to the SCN [49]. Approximately 50% of blinded individuals have disturbed sleep [50, 51]. Rarely, sighted individuals are affected as well [52, 53].

### **Diagnosis of Free-Running Type**

Individuals with a free-running type circadian rhythm disorder will exhibit short periods of normal sleep duration alternating with longer periods of short sleep, excessive daytime sleepiness and daytime napping [53, 54]. Symptoms may be less severe in individuals who time their sleep–wake cycle to correspond with their endogenous, free-running rhythm. Diagnosis is based on a detailed sleep history

suggestive of a gradual delay in the sleep–wake cycle [55]. Sleep diaries and actigraphy can be helpful in establishing the diagnosis [29, 56].

### **Treatment of Free-Running Type**

Although light is the strongest synchronizer of the circadian clock, non-photic signals also can entrain the endogenous circadian rhythm. Exogenous melatonin, exercise, timing of meals, and an imposed sleep–wake schedule can also entrain the circadian rhythm, albeit weakly compared to light [49]. Therefore it seems reasonable that adhering to a scheduled sleep–wake routine with scheduled meals during the day will promote entrainment to a 24 h period in free-running individuals, although there is no published evidence to support this assertion.

Exogenous melatonin has been reported to entrain free-running individuals [51, 53, 57]. As mentioned above, the free-running sleep–wake cycle gradually delays, and free-running individuals intermittently experience a temporary period of normal sleep. During this period of normal sleep, daily administration of low dose melatonin 0.5 mg at bedtime (during the advance phase of the melatonin phase-response curve) can successfully entrain the circadian rhythm to a 24 h period [49, 58]. The efficacy of melatonin-receptor agonists, such as ramelteon and agomelatine, in free-running type is currently unknown.

### ***Irregular Sleep–Wake Rhythm***

An irregular sleep–wake pattern is characterized by the absence of an observable circadian rhythm where three or more short periods of sleep and wake are randomly dispersed throughout the 24 h period. Typically, each of the sleep and wake periods lasts for approximately 1–4 h. The prevalence of irregular sleep–wake rhythm is higher in older adults and is attributed to a variety of factors including an age-related reduction in circadian neuronal activity, decreased sensitivity and exposure to light, and reduced daytime physical and social activity [59]. Older individuals with neurodegenerative disorders, such as Alzheimer’s disease, and who are institutionalized due to poor physical health are at higher risk for irregular sleep–wake rhythm [59]. Individuals with traumatic brain injury and mental retardation may also be at increased risk [59].

### **Diagnosis of Irregular Sleep–Wake Rhythm**

A clinical history of fragmented, short sleep interspersed with short periods of wake is suggestive of an irregular sleep pattern. Reports of insomnia during the night and excessive sleepiness and frequent napping during the day are common. There should be three or more short sleep and wake periods throughout a 24 h period, each lasting

for only several hours [55]. A sleep diary or actigraphy for 1–2 weeks can be helpful in establishing a diagnosis [29, 56]. A detailed sleep evaluation to determine the presence or absence of other sleep disorders, such as sleep disordered breathing, is essential in these patients.

### **Treatment of Irregular Sleep–Wake Rhythm**

In order to promote sleep consolidation at night and wakefulness during the day, enhancing exposure to a variety of time cues is essential. These cues include a regularly scheduled bedtime and wake time, light therapy during the day, exogenous melatonin at bedtime, and scheduled physical and social activities. Structured daytime physical and social activities as well as a scheduled sleep and wake routine can promote consolidated nighttime sleep and improve daytime wakefulness [60]. Since light is the strongest time cue, maximizing bright light exposure during the daytime can decrease daytime napping and promote consolidated sleep. In one study, bright light therapy for 2 h in the morning improved nighttime sleep and reduced daytime sleeping in patients with dementia [61]. Exogenous melatonin at bedtime when combined with light therapy may promote consolidated nighttime sleep [62]; however, the efficacy of melatonin alone has not been consistent [63–65]. One study showed that melatonin plus light therapy was associated with improved sleep and cognitive performance in elderly subjects with dementia; however, melatonin treatment without light therapy was associated with withdrawn behavior and mood disturbance [66]. Until more research is available, it seems reasonable that for most elderly patients with dementia, melatonin should be used in combination with bright light therapy rather than alone. Avoidance of light and loud noise in the late evenings and nighttime is recommended [67].

### ***Shift Work Disorder***

Shift work sleep disorder occurs when the patient's work schedule overlaps with the normal sleep cycle. In certain individuals, this overlap may result in excessive sleepiness during work hours and insomnia when attempting to sleep during off hours. Studies suggest that sleep is shortened by 2–4 h in night shift workers compared to day workers with a reduction in stage 2 and stage REM sleep [68, 69]. This is likely due to a heightened alerting signal from the endogenous circadian clock interfering with day sleep. Consequently, shift workers often suffer sleep disruption and are at increased risk for excessive sleepiness during work, errors in judgment, impaired job performance, and serious accidents compared to day workers [70–72]. Approximately 20% of the workforce in industrialized countries are shift workers, and one study estimated that the prevalence of shift work sleep disorder is 10% among night and rotating workers [73]. Rotating shift workers may be at increased risk for shift work disorder compared to night workers, presumably from lack of adjustment to a fixed schedule [74].

## Diagnosis of Shift Work Disorder

Sleep disturbances and sleepiness are common in shift workers. It has been reported that 40–80% of night and rotating shift workers suffer sleep complaints [55], but not all of these complaints are necessarily secondary to shift work. Therefore an important challenge facing clinicians is to distinguish those who have excessive sleepiness and insomnia due to shift work intolerance and those who have sleep complaints related to a separate sleep disorder. Obtaining a detailed sleep history for symptoms of sleep disordered breathing, other hypersomnia and insomnia disorders, and movement disorders such as restless legs syndrome is critical [74].

Common symptoms of shift work disorder are excessive sleepiness at work and insomnia or insufficient sleep between shifts. Problems with performing work duties and falling asleep during work shifts are frequently present [74]. Social relationships of shift workers may be strained from misalignment of work and sleep schedules with day-oriented social and family schedules [75]. Gastrointestinal complaints, such as irritable bowel syndrome and peptic ulcer disease, are also more prevalent in shift workers [73, 76, 77]. Although sleep disturbance and fragmentation may be present, more commonly shift workers complain of shortened or insufficient sleep [78]. In addition to a detailed history, sleep diaries or actigraphy may be useful in establishing the diagnosis of shift work disorder by demonstrating shortened sleep or sleep disruption between work shifts [29, 56].

## Treatment of Shift Work Disorder

The approach to treating shift work disorder should be multi-faceted and tailored to the patient's needs, preferences, family and social responsibilities, and work schedule. There are three main strategies that warrants review: (1) Improve circadian alignment with sleep and shift work schedules; (2) improve sleep (using cognitive-behavioral therapy, melatonin, and hypnotics); and (3) enhance alertness with scheduled naps and wake-promoting agents.

The first strategy is to improve circadian alignment with work and sleep schedules. Because the primary underlying etiology of shift work disorder is circadian misalignment, strategies to realign the circadian clock with the sleep/wake/work schedule may reduce excessive sleepiness during shift work and improve sleep. Since light is the strongest synchronizing agent for the circadian clock, appropriately timed exposure to bright light can help accelerate and maintain circadian alignment in shift workers [34, 79]. In night shift workers, the goal is to delay circadian rhythms so that the sleep period occurs during the day and wakefulness is maintained during the night work period. This is referred to as *adaptation* [80]. A number of studies have shown that several hours of either intermittent or continuous light exposure ranging from 2,500 to 9,500 lx given during the night shift results in improved alertness during the shift and accelerated circadian realignment [81–84]. One simulated night shift study found that five light treatments (approximately 4,100 lx), each lasting 15 min and separated by 45-min intervals, were effective in delaying DLMO and was associated with improved performance measures using the Automated

Neurophysiological Assessment Metrics (ANAM) test battery [85]. Subjects who did not have a significant delay in DLMO were more likely to have reduced total sleep times [85]. In addition to increasing light levels during the night, it is also important to avoid morning light by using goggles or sunglasses in the morning following the night shift, because exposure to light in the early morning could advance the timing of circadian rhythms and prevent adaptation [84–86]. However, for many shift workers, the demands of job responsibilities may render light therapy inconvenient and unfeasible, and adequate light sources may not be widely available.

The second strategy is to improve sleep quality and increase sleep time with behavioral strategies and medications. Adherence to principles of good sleep hygiene and treatment of comorbid sleep disorders, such as insomnia, sleep apnea, and restless legs, are essential. Good sleep hygiene includes adhering to a regular wake and sleep schedule, daily exercise, and avoiding excessive caffeine, nicotine, and alcohol close to bedtime [87]. These healthy behaviors can help improve sleep quality, maintain circadian alignment, and prevent the development of factors that precipitate and perpetuate insomnia.

A number of studies have evaluated the use of hypnotics on sleep under simulated shift work conditions. Although several hypnotics, such as zopiclone [88, 89], triazolam [90], and zolpidem [91–93] have been shown to improve daytime sleep quality in some subjects, these medications are not approved by the U.S. Food and Drug Administration (FDA) for this purpose. Use of these medications should be done with caution given the potential adverse consequences of long-term hypnotic use and carryover sedation. Melatonin, on the other hand, has a largely benign safety profile. Exogenous melatonin (1–3 mg), when given before bedtime, has been shown to modestly improve day sleep quality and duration in some but not all shift workers [29, 83, 94]. Although melatonin has not been approved by the FDA for the treatment of CRSD, exogenous melatonin is generally well tolerated with only mild side effects. The most commonly reported side effects include drowsiness, fatigue, and nausea [95].

The third strategy and perhaps from a functional and safety perspective is to enhance alertness with scheduled naps and when needed wake-promoting agents. Scheduled naps have been shown to be effective in reducing sleepiness in shift workers. An afternoon 1–2 h nap prior to a night shift and short naps during the work shifts can reduce sleepiness and improve cognitive function [96–99]. Shorter naps of 10–20 min are typically recommended to avoid the grogginess that accompany longer sleep periods, although the optimal amount of nap time needed has not been established and likely varies depending on the individual [96, 97, 100].

Caffeine is a widely available and inexpensive medication that is effective in improving wakefulness in shift workers. Studies have shown that 150–400 mg of caffeine reduces sleepiness, increases subjective alertness, and improves performance during the night shift [101]. The effectiveness of caffeine is enhanced when combined with naps [102]. Modafinil is a wake-promoting medication approved by the FDA for excessive sleepiness in shift workers. Studies have shown that modafinil improves alertness and quality-of-life scores in shift workers and is generally well tolerated [103–105]. Headache and nausea are the most common side effects, and serious side effects are rare. However, there is one published case report of a woman

with no previous psychiatric history, who developed psychosis while taking modafinil under simulated shift work conditions [106]. Recently, armodafinil (containing the *R*-isomer of modafinil only, giving rise to more sustained action instead of both *R* and *S* isomers as in modafinil) 150 mg 1 h before shift work was shown to improve wakefulness, increase mean sleep latency and improve neurocognitive function in permanent night and rotating shift workers [107]. However, it is important to note that although wake-promoting medications improve function, alertness level does not normalize and many workers remain excessively sleepy during the work shift. Therefore, adherence to good sleep hygiene, behavioral and environmental approaches to enhance circadian alignment, as well as counseling on safety precautions are essential for all patients.

## ***Jet Lag***

Jet lag occurs when the endogenous circadian rhythm becomes misaligned with the external light–dark cycle due to travel across time zones. Symptoms are generally temporary and include nighttime insomnia and excessive daytime sleepiness. International travel across transmeridian lines is common. In 2007, it was reported that 31 million U.S. travelers went overseas, many to Europe and Asia [108]. Jet lag can have adverse effects on alertness, mood, and cognitive and physical performance, which have important consequences for travelers involved in the fields of business, military, and athletics [109–113].

## **Diagnosis of Jet Lag**

The symptoms of jet lag are often predictable depending on the direction of travel. Individuals flying east develop symptoms similar to delayed sleep phase. Difficulty falling asleep in the evenings and excessive sleepiness in the mornings is common. Conversely, individuals flying west develop symptoms similar to advanced sleep phase and include excessive sleepiness in the early evenings and early awakenings in the middle of the night or morning. Symptoms are temporary and eventually wane as the endogenous circadian rhythm adjusts to the external light–dark cycle. Symptoms of jet lag are generally more pronounced and adjustment prolonged for eastward travelers compared to westward travelers. This is because the endogenous circadian rhythm is >24 h, and it is easier to adjust to westward travel by phase delay as opposed to eastward travel, which requires a phase advance [55].

## **Treatment of Jet Lag**

Symptoms of jet lag improve as the endogenous circadian rhythm gradually adjusts to the external environment. Treatment of jet lag involves accelerating this adjustment

with appropriately timed exposure to light and melatonin as well as a number of behavioral strategies. Behavioral strategies include avoiding excessive caffeine and alcohol during travel to reduce travel fatigue, eat meals at local times, and engage in good sleep hygiene [114].

For eastward travelers, appropriately timed exposure to light and melatonin to advance the endogenous circadian clock will accelerate alignment and improve symptoms of jet lag. Early morning light exposure and avoidance of light in the evenings will promote advancement of the circadian rhythm [114]. Melatonin 0.5–5 mg taken at bedtime local time may also promote advancement of the endogenous circadian clock [115, 116]. Advancing the endogenous circadian clock prior to traveling east has also been proposed as a strategy to reduce jet lag symptoms [117, 118]. In one study, subjects advanced their typical morning wake up times by 1 or 2 h each day for 3 days [118]. During those 3 days after awakening, subjects were exposed to a total of 2 h of light treatments (four 30 min treatments at approximately 5,000 lx separated by 30 min of ordinary room light) [118]. Phase advancement of approximately 1.4–1.9 h was achieved [118]. Although this was not a field study, phase advancement prior to eastward travel may significantly reduce jet lag symptoms [118].

For westward travelers, appropriately timed exposure to light and melatonin to delay the endogenous clock will accelerate alignment. Maximizing light exposure in the evenings and avoiding morning light will promote a delay in the circadian rhythm. Melatonin in the mornings may also accelerate circadian delay but may result in sleepiness during the day. The soporific effects of melatonin may limit its use in this setting [108].

Symptomatic treatment of insomnia symptoms and excessive daytime sleepiness secondary to jet lag with naps, caffeine, hypnotic, and wake-promoting medications may also be useful. In order to improve sleep, 5 mg of melatonin for 4 days at bedtime local time has been shown to be beneficial [116, 119]. Zolpidem has also been shown to reduce symptoms of sleep disturbance [120, 121]. In subjects traveling east over five time zones, ramelteon, a melatonin-receptor agonist, given at bedtime was demonstrated to reduce sleep latency compared to placebo [122]. Caffeine has been shown to improve wakefulness during the day in the setting of jet lag [119]. In subjects flying eastward from the U.S. to France (6 h time zone change), armodafinil 150 mg was demonstrated to be effective in improving wakefulness during the day and modestly increased mean sleep latency compared to placebo [123]. Headache, nausea, and diarrhea were the most common side effects [123].

## Summary

Among its influence on many physiological functions, the circadian system regulates the sleep/wake cycle. CRSDs result from alterations in the endogenous circadian system or misalignment of the endogenous circadian rhythms with the external environment. Although treatment of CRSDs can include pharmacotherapy, lifestyle, and behavioral changes to optimize circadian alignment and sleep quality are essential



for everyone. Recent molecular research has shed light on genetic causes of CRSDs that may lead to novel and targeted therapeutic options for these under-recognized disorders.

## Summary of Keypoints

- The sleep/wake cycle is the most outward display of circadian rhythm generated by the master clock in the brain. CRSDs can occur when the timing of the central clock is out of synchrony with the conventional schedule (e.g., sleep phase disorders, free-running, irregular sleep wake rhythm) or when there is misalignment between the normal intrinsic rhythm and the 24-h external environment (e.g., jet lag and shift work). The most commonly encountered CRSDs are the sleep phase disorders (advanced and delayed), shift work sleep disorder and jet lag disorder.
- Sleep phase disorder are characterized by inability to initiate sleep or wake up at conventional times, resulting in insomnia or daytime sleepiness which interferes with the patient's life. Genetic polymorphisms of clock genes have been discovered in patients.
- Treatment of delayed and ASPD involves advancing or delaying the sleep phase with bright light therapy and/or melatonin, as well as behavioral changes. Specific timing of bright light and melatonin therapy is dependent on the phase of each patient's circadian rhythm.
- Shift work sleep disorder occurs when the patient's work schedule overlaps with the normal sleep cycle, resulting in excessive sleepiness during work hours and insomnia when attempting to sleep during off hours.
- Management of shift work sleep disorder involves improving circadian alignment with sleep and shift work schedules, improving sleep with behavioral therapy, melatonin, and hypnotics, and enhancing alertness with scheduled naps and wake-promoting agents.
- Jet lag can have adverse effects on alertness, mood, and cognitive and physical performance, and symptoms are generally more pronounced and adjustment prolonged for eastward travelers compared to westward travelers.
- Symptoms of jet lag can potentially be mitigated by pre-travel phase shifting with bright light therapy so that the sleep/wake cycle is more aligned to day and night at destination. Alternatively, bright light and melatonin therapies can be used upon arrival.

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# Chapter 16

## Narcolepsy and Idiopathic Hypersomnia

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**Keywords** Narcolepsy • Idiopathic hypersomnia • Symptoms • Epidemiology  
• Pathophysiology • Diagnosis • Differential • Pediatric • Treatment

### Introduction

Excessive daytime sleepiness (EDS) is a common symptom that is part of many different medical, neurologic, psychiatric, and sleep disorders. The terms “excessive daytime sleepiness” and “hypersomnia” are often used interchangeably; however, the term “hypersomnia” should be reserved to refer to a group of disorders in which the primary complaint is excessive sleepiness. Two of these disorders, narcolepsy and idiopathic hypersomnia, are considered to be hypersomnias of central origin and will be discussed here.

Narcolepsy was originally described by Gelineau in 1880 as a disorder involving excessive sleepiness and sleep attacks associated with a variety of emotional states. He also described episodes of falls or “astasia” which was later termed cataplexy. Since this time (especially over the last 5 years), a number of advances in our understanding of narcolepsy have been made. For instance, the discovery of the association between narcolepsy and the Human Leukocyte antigens (HLA) DRB1\*1501/DRB1\*1503 and with DQB1\*0602 suggested an autoimmune process. Also, the discovery by two independent groups in 2005 of a reduction in the neuropeptide, hypocretin/orexin, is believed to be responsible for many of the symptoms of narcolepsy. Additionally, in 2005, the *International Classification of*

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*Sleep Disorders*, second edition (ICSD-2) categorized narcolepsy into three different types: narcolepsy with cataplexy, narcolepsy without cataplexy, and narcolepsy due to a medical disorder. The ICSD-2 characterized narcolepsy by symptoms of excessive sleepiness as well as the pathologic manifestations of REM sleep, such as cataplexy, sleep paralysis, and hypnagogic hallucinations.

The term “idiopathic hypersomnia” was first used in 1976 by Bedrich Roth to describe a disorder with both a monosymptomatic and a polysymptomatic form. The monosymptomatic form exhibits only EDS, whereas the polysymptomatic form manifests not only symptoms of EDS, but also a long duration of the major sleep period, and a prominent sleep inertia upon awakening. Unlike narcolepsy, there is relatively limited research on the pathophysiology or the spectrum of symptoms of idiopathic hypersomnia. In 2005, the ICSD-2 classified idiopathic hypersomnia into two types, one associated with a prolonged sleep episode at night, which is called idiopathic hypersomnia with long sleep time, and another that has a normal duration of sleep at night called idiopathic hypersomnia without long sleep time.

## Clinical Features

### *Narcolepsy*

Narcolepsy is described as a syndrome consisting of EDS (including periods of irresistible sleep), cataplexy, sleep paralysis, and hypnagogic hallucinations; additional features include automatic behaviors and fragmented or disrupted nighttime sleep. The effects of narcolepsy are largely manifested during periods of wakefulness, i.e., features of REM sleep intrude into wakefulness.

Narcolepsy typically begins with the symptom of excessive sleepiness and other symptoms of variable severity can develop slowly, suddenly, or not at all. Occasionally, cataplexy can develop first and then later be followed by the development of excessive sleepiness; this is especially true in children, where sleepiness is disguised as behavioral abnormalities [1]. Narcolepsy patients often have an irresistible urge to sleep, which often occurs at inopportune times whether it is during monotonous sedentary tasks or while performing mentally or physically demanding activities. For instance, they can fall asleep while eating, while sitting at a meeting, during phone conversations, during sexual intercourse, or while driving a car. These sleep episodes occur about 3–5 times/day in most patients and usually vary from a few minutes to several hours in duration [2]. Patients often report that after these sleep episodes or after taking scheduled naps, they wake up feeling refreshed and may not feel sleepy again for up to a few hours later; however, there are also many patients who indicate persistent (although perhaps somewhat improved) sleepiness despite taking these naps. Patients can also experience microsleep events, which are seconds or less of sleep that intrude into the waking state. Upon awaking from these episodes, the patients may not be aware that they were

asleep and continue the activity they were performing prior to the sleep event. It is likely that such episodes are at least partially associated with patients' complaints of difficulty concentrating, inattention, or memory impairment.

In children, it is difficult to identify classic narcolepsy symptoms since many are not able to provide an accurate history of cataplexy, hypnagogic hallucinations, or sleep paralysis. Sleepiness may also manifest as behavioral problems, decreased performance, inattentiveness, lack of energy, or bizarre hallucinations that makes it even more difficult to diagnose narcolepsy. Furthermore, when excessive sleepiness is present, it can often be mistaken for normal behaviors in children of preschool age, as they usually take habitual naps. Occasionally in school-aged children, excessive sleepiness can be identified when there is a reappearance of daytime naps in a child who had previously discontinued regular napping [3].

Cataplexy is the most specific symptom of narcolepsy consisting of an abrupt, bilateral (occasionally unilateral) loss of skeletal muscle tone. It is usually triggered by the occurrence of sudden emotion such as laughter or humorous experiences; sometimes even the memory of a humorous event can precipitate an attack. Other triggers for cataplexy include anger, embarrassment, surprise, stress, or even sexual arousal [4]. During a cataplexy attack, which can last up to several minutes, the patient is unable to move; however, the diaphragm and ocular muscles are unaffected. During this time, the patient remains awake, aware of their surroundings and able to remember the details of the event. If the attack is prolonged, however, sleep can follow. More commonly, attacks of cataplexy are partial, affecting only certain muscle groups, such as the arms, neck, or face. During partial cataplexy attacks, the jaw may sag, the head can droop, and speech may become garbled [5]. In children, atypical manifestations of cataplexy can include blurred vision, irregular breathing, sudden loss of smiling, or "semipermanent eyelid and jaw weakness" [6].

Sleep related hallucinations, sleep paralysis, and automatic behaviors are common manifestations of many disorders that disrupt/fragment sleep and cause excessive sleepiness, including narcolepsy and idiopathic hypersomnia [7]. Similar to cataplexy, patients with sleep paralysis experience a brief loss of voluntary muscle control with an inability to move or speak, but retain awareness during the event. Unlike, cataplexy, these episodes are not provoked by intense emotion or stress. The phenomena usually occur during sleep–wake transitions and are often associated with fearful hypnopompic or hypnagogic hallucinations. The events typically remit on their own within 1–10 min, but can also be terminated when someone touches the patient [8].

The hypnagogic and hypnopompic hallucinations can also occur independently of the sleep paralysis episodes. They are intense dream-like states that occur when falling asleep (hypnagogic) or when awaking from sleep (hypnopompic) [8]. The hallucinations are usually visual or auditory and occasionally involve other senses, e.g., tactile or vestibular. They are occasionally pleasant, but quite often frightening or disturbing to the patient. The visual hallucinations can consist of simple forms, such as circles or multisided geometric figures or can be more intricate such as animals or people. Similarly, the auditory hallucinations can manifest as simple

sounds, such as knocking on a door or a phone ring, or more complex tunes, such as a musical composition. Less often, patients report hallucinations such as smelling a scent/odor, or having a sense that one is falling, or feeling that someone or something is touching them.

Automatic behavior is the performance of simple or complex routine tasks by individuals who remain unaware of the activity. These behaviors range from activities such as talking on the phone or writing to walking, cooking, or driving. Some patients report that they have ordered items through the phone, or cooked a meal, and did not remember doing so. Some also report driving home from work and not realizing how they got there. The personal and public hazards of such behaviors are self-evident.

In addition to episodes of EDS, narcolepsy patients also report difficulty in maintaining sleep at night due to a dysfunction of central sleep regulation which causes frequent transitions between sleep and wakefulness throughout the entire 24-h cycle. They report frequent nocturnal awakenings and occasionally indicate that they do not sleep for long periods during the night.

### ***Idiopathic Hypersomnia***

Similar to narcolepsy, patients with idiopathic hypersomnia also have symptoms of excessive sleepiness. Those with the long sleep time type have a prolonged major sleep period of 10 h or longer with few or no awakenings. They report often having an irresistible urge to take prolonged naps (up to 3–4 h in duration) during the day and typically awaken unrefreshed. These patients also experience difficulty waking up in the morning and at the end of a nap [3, 7, 9].

Analogous to idiopathic hypersomnia with long sleep time, patients with idiopathic hypersomnia without long sleep time have symptoms of excessive sleepiness. They also take prolonged nonrefreshing naps and have difficulty awakening from sleep periods, albeit it is typically less laborious than in the long sleep time type. The duration of the major sleep period in these patients, however, although occasionally prolonged is by definition less than 10 h [3, 6, 9].

In a report by Bassetti and Aldrich in 1997 [9], some patients with idiopathic hypersomnia with and without long sleep time were noted to have orthostatic hypotension, headaches, as well as cold hands and feet (Raynaud's type phenomena). Additionally, as mentioned earlier, hypnagogic hallucinations and sleep paralysis may be present. These patients often never feel fully alert, even after their normal or prolonged sleep period. They often require multiple alarm clocks to awaken in the morning or after naps, but usually end up becoming dependent on other people to awaken them. The difficulty awakening is followed by, or is at least partially attributed to, a state of sleep drunkenness. Simply stated, sleep drunkenness is the confusion and behaviors a normal person may experience if abruptly awoken from deep sleep. Patients are confused upon awakening and are unable to perform tasks or react appropriately [7, 9].

## Epidemiology

### *Narcolepsy*

Due to the overlap of clinical symptoms and polysomnographic/multiple sleep latency test (MSLT) features with other conditions such as depression, other sleep disorders or even with normal individuals, it is difficult to make an accurate assessment of the true prevalence of narcolepsy. It is estimated that less than 50% of patients with narcolepsy have been diagnosed [10, 11]. Nevertheless, narcolepsy has been documented to begin at any age from infancy (rarely) to as late as old age, but most commonly within the first two decades of life. It affects both men and women equally with an approximate prevalence of 1 in 2,000 people (0.05%) in the United States [12].

There appears to be a genetic, racial, and ethnic predisposition for the development of narcolepsy [13]. The risk of a first-degree relative developing narcolepsy with cataplexy is approximately 1–2%, which is prominently higher than that estimated for the general population [14]. In addition, the HLA subtypes DR2 (DRB1\*1501) and DQ (DQB1\*0602) have also been found to be closely associated with narcolepsy. The HLA marker, DQB1\*0602 has a prevalence ranging from 85 to 95% in patients with narcolepsy with cataplexy and about 40% in patients with narcolepsy without cataplexy vs. about 26% in the general population [15]. A review of the literature indicates that the prevalence of narcolepsy/cataplexy ranges from a low of 0.002% among Israeli Jews to a high of 0.15% among the Japanese general population. More recently, a general population study with a representative sample of over 18,000 subjects in five European countries estimated a prevalence of 0.047% [3].

The prevalence of cataplexy among patients with narcolepsy varies widely with estimates ranging from 60 to 90% [16] of narcoleptics. Patients with cataplexy generally report that this symptom remains persistent with only minor fluctuations in severity; however, the severity and frequency of attacks may vary widely and range from occasional to multiple attacks daily. A few patients have reported spontaneous remission of cataplexy attacks. It has been suggested that a decline in cataplexy over time represents the ability of patients to adapt to their illness and learning to avoid those situations where cataplexy is most likely to occur.

### *Idiopathic Hypersomnia*

More challenging than assessing the prevalence of narcolepsy is that of determining the prevalence of idiopathic hypersomnia. The reported prevalence in clinic populations when compared to narcolepsy patients widely varies depending upon the literature reviewed [6, 17–19]. At least part of the difficulty in determining idiopathic hypersomnia's prevalence is due to its nosological ambiguity. There has also been a propensity

to label all difficult-to-classify cases of EDS as idiopathic hypersomnia [20]. Since the ICSD-2 classification scheme was developed, there have not been any systematic prevalence studies for idiopathic hypersomnia. Accordingly, it is safe to say that the true prevalence of idiopathic hypersomnia is unknown. What we do know is that there appears to be a female predominance [21] with the age of onset ranging from birth to early adulthood [22]. Some earlier studies also suggest an autosomal dominant mode of inheritance [23].

## Pathophysiology

### *Narcolepsy*

As mentioned earlier, there is a higher occurrence of HLA DQB1\*0602 in narcolepsy patients than in the general population. It is suspected that patients with this HLA marker (and likely other currently unknown genetic links) may possess a genetic susceptibility for some event that leads to the development of narcolepsy. Environmental factors such as infections [24, 25], head trauma [26], or even a change in sleeping habits [25] have been associated with the onset of narcolepsy.

The discovery of the neuropeptide hypocretin [27, 28] has greatly enhanced our understanding of the pathophysiology of narcolepsy. Hypocretin-containing neurons are located in the perifornical and lateral hypothalamus where they project widely to communicate with numerous brain nuclei including those responsible for the regulation of sleep, alertness, and muscle tone. Evidence suggests that most cases of narcolepsy with cataplexy are associated with loss of hypocretin-containing hypothalamic neurons and cases of narcolepsy without cataplexy may be caused by a partial loss of these neurons. Thannickal et al. [29] and Mignot et al. [30] reported an 85–95% loss of hypocretin-containing neurons in narcolepsy with cataplexy patients that corresponded to the finding of low or undetectable concentrations ( $\leq 110$  pg/mL) of hypocretin in the cerebrospinal fluid (CSF) of these patients. More recently, Thannickal et al. [31] found a loss of about a third of the hypothalamic hypocretin-containing cells in one patient with narcolepsy without cataplexy. An autoimmune process may be responsible for the loss of the hypocretin neurons; however, antibodies to hypocretin and hypocretin receptors have not been found [32–35].

Recently, additional support for the autoimmune etiology hypothesis was discovered. Increased antistreptococcal antibodies were reported in patients with recent onset of narcolepsy, suggesting streptococcal infections may be an inciting event that is initiating an autoimmune process [24, 36]. Hallmayer et al. [37] also found a strong association between narcolepsy and a polymorphism in the T-cell receptor alpha locus (another indication that an autoimmune process has a role). Earlier in 2010, elevated Tribbles homolog 2 (Trib2) specific antibodies levels were discovered in patients with narcolepsy. Trib2 was previously known as an autoantigen in autoimmune uveitis; it has been identified in hypocretin neurons of a transgenic mouse model. In narcolepsy patients, titers of Trib2-specific antibodies were highest soon after narcolepsy onset and then decreased within the first 3 years of the

disorder and finally stabilized at levels much higher than that of controls (normal controls and patients with idiopathic hypersomnia, multiple sclerosis, or other inflammatory neurologic disorders) [38]. This finding provides exciting evidence that narcolepsy is an autoimmune disorder; however, more work needs to be done to establish a causal pathogenic role of the antigen and antibodies.

## *Idiopathic Hypersomnia*

In comparison to narcolepsy, less is known about the pathophysiology of idiopathic hypersomnia with or without long sleep time. One possible reason for this is that there are no specific criteria, clinical or polysomnographic, that is pathognomic or even partially characteristic of the disorder, such as cataplexy or sleep onset REM periods are for narcolepsy. There is no clear association with CSF hypocretin levels [39] as in narcolepsy. Although there appears to be a strong genetic component suggested by the high proportion of familial cases, no associated genes have been identified. Studies with HLAs have also found no connection [9].

Some early studies suggested that monoamine metabolites had a role in the etiology of idiopathic hypersomnia [40–42] and more recently, Bassetti et al. [43] have revisited the possible association of dopamine with idiopathic hypersomnia; however, further studies to assess the validity of these hypotheses need to be done.

There is a possible common pathway between the pathophysiology of narcolepsy and idiopathic hypersomnia. A low CSF histamine level has been identified in both these disorders and has not been seen in patients with excessive sleepiness due to sleep apnea [44, 45]. Accordingly, it is hypothesized that low histamine may be specific to hypersomnias of central origin [45]. In addition, since idiopathic hypersomnia hypocretin levels are normal, it has been suggested that factors other than hypocretin deficiency are the cause of these low histamine levels. Further research still needs to be done to validate this hypothesis and to better understand the role of histamine in these disorders.

## **Diagnosis**

### *Narcolepsy*

There are three main types of narcolepsy: narcolepsy with cataplexy, narcolepsy without cataplexy, and secondary narcolepsy (Table 16.1). Narcolepsy with cataplexy is defined as excessive sleepiness that occurs for at least 3 months associated with definite cataplexy. The diagnosis may be confirmed by polysomnography followed by a MSLT [46]. Alternatively, a low CSF hypocretin level ( $\leq 110$  pg/mL or one third of mean normal control values) is diagnostic [27]. The polysomnography should confirm at least 6 h of sleep and exclude other sleep disorders that could account for the symptoms, such as obstructive sleep apnea syndrome. It usually

**Table 16.1** Diagnostic criteria for narcolepsy

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Narcolepsy with cataplexy	
1.	At least 3 months of excessive daytime sleepiness (EDS)
2.	Cataplexy is present
May be confirmed by	
3.	PSG followed by a multiple sleep latency test (MSLT) <i>or</i>
a.	The PSG should rule out other causes of disrupted nocturnal sleep and demonstrate at least 6 h of sleep
b.	The MSLT should show a sleep latency of $\leq 8$ min and two or more sleep onset REM periods
4.	A cerebrospinal fluid (CSF) hypocretin-1 level $\leq 110$ pg/mL
Narcolepsy without cataplexy	
1.	At least 3 months of EDS
2.	Cataplexy is absent; however, questionable or atypical cataplexy-like episodes can be present
Must be confirmed by	
3.	PSG followed by a MSLT
a.	PSG rules out other causes of disrupted nocturnal sleep and demonstrates at least 6 h of sleep
b.	MSLT shows a sleep latency of $\leq 8$ min and two or more sleep onset REM periods
Narcolepsy due to a medical condition	
1.	At least 3 months of EDS
2.	A significant underlying medical or neurologic condition accounts for the daytime sleepiness
3.	A definite history of cataplexy is present <i>or</i>
4.	If cataplexy is absent and/or questionable or atypical cataplexy-like episodes are present then a PSG followed by a MSLT should be done
a.	PSG rules out other causes of disrupted nocturnal sleep and demonstrates at least 6 h of sleep
b.	MSLT shows a sleep latency of $< 8$ min and two or more sleep onset REM periods
5.	If either condition 3 or 4 above is not met, CSF hypocretin-1 levels must be $\leq 110$ pg/mL (or 30% of normal control values) in a noncomatosed patient

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Adapted from American Academy of Sleep Medicine [3]

demonstrates a short sleep latency and fragmented nocturnal sleep and may show early REM sleep onset and increased stage 1 sleep [47]. The MSLT should exhibit two or more sleep onset REM periods with a mean sleep latency of  $\leq 8$  min [3].

Patients who do not have cataplexy or have atypical cataplexy-like events, and other sleep disorders have already been excluded, require confirmatory sleep studies, i.e., nocturnal polysomnography followed by an MSLT, for the diagnosis. CSF hypocretin-1 levels are usually normal in these patients [18, 27]; therefore, it is usually not indicated. CSF hypocretin-1 levels may be done, however, for patients with atypical cataplexy-like episodes for whom a diagnosis of narcolepsy with cataplexy is being entertained. It can also be done for pediatric patients with suspected narcolepsy, especially if the MSLT is inconclusive, to make the diagnosis. Such studies are also required to establish the diagnosis of secondary narcolepsy that temporally occurs with an underlying neurological disorder.

As mentioned earlier, it is difficult to identify classic narcolepsy symptoms in children. The diagnosis can be made clinically if definite cataplexy is present or with the assistance of the MSLT or by measurement of CSF hypocretin-1 levels. A PSG followed by an MSLT can help objectively assess sleepiness in a child; however, normal values on sleep studies, especially for MSLTs, have not been



**Table 16.2** Diagnostic criteria for idiopathic hypersomnia

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Idiopathic hypersomnia with long sleep time

1. At least 3 months of EDS
2. Interview, actigraphy, or sleep logs demonstrates over 10 h of nocturnal sleep with
  - a. Difficulty awaking in the morning
  - b. Difficulty awaking at the end of naps
3. PSG performed
  - a. Rules out other causes of sleepiness
  - b. Shows a short sleep latency
  - c. Shows a major sleep period greater than 10 h
4. MSLT, if done, shows
  - a. A mean sleep latency of <8 min
  - b. Less than two sleep onset REM periods

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Idiopathic hypersomnia without long sleep time

1. At least 3 months of EDS
  2. Interview, actigraphy, or sleep logs demonstrates normal sleep period (more than 6 h and not over 10 h)
  3. PSG performed
    - a. Rules out other causes of sleepiness
    - b. Shows a major sleep period that is normal in duration (more than 6 h but not over 10 h)
  4. MSLT, if done, shows
    - a. A mean sleep latency of <8 min
    - b. Less than two sleep onset REM periods
- 

Adapted from American Academy of Sleep Medicine [3]

standardized in subjects younger than 8 years of age and results should be interpreted with care. Carskadon [48] suggested using a child's Tanner stage of sexual development to compare sleep study results to normal values of nocturnal total sleep time, daytime sleep latency, and daytime REM sleep latency as these are closely linked to the Tanner stages. As suggested earlier, HLA testing (in a child or adult) is not a useful screening or diagnostic tool; however, it might be useful in atypical narcolepsy with cataplexy presentations. A negative test should encourage the physician to make certain that other sleep disorders are excluded before assigning a diagnosis of narcolepsy.

## ***Idiopathic Hypersomnia***

In contrast to narcolepsy, idiopathic hypersomnia has only two types: one with a long sleep time and one without a long sleep time (Table 16.2). In order to make this diagnosis, the associated excessive sleepiness, similar to narcolepsy, needs to occur almost daily for at least 3 months. In patients with the "long sleep time type," the nocturnal sleep is more than 10 h long and there is difficulty awaking from the sleep period including any naps. In the "without long sleep time type," the nocturnal sleep period is greater than 6 h but less than 10 h. Polysomnography demonstrates these sleep times and should rule out other causes (e.g., sleep apnea) of excessive sleepiness. An MSLT performed following the nocturnal polysomnography should show a



mean sleep latency of less than 8 min with less than two sleep onset REM periods [3]. In patients with long sleep time, however, awaking the patient in the morning following an overnight polysomnogram to do a MSLT does not allow for the documentation of the prolonged sleep time. Moreover, the short naps scheduled every 2 h do not allow for the demonstration of prolonged unrefreshing naps. Accordingly, alternate nonvalidated means for diagnosis have been suggested by some authors, including extended (24 h or longer) polysomnography or actigraphy [7]. In patients without long sleep type, the MSLT is currently the primary way to differentiate these patients from patients with narcolepsy without cataplexy.

## Differential Diagnosis

Excessive sleepiness is common to many sleep disorders, besides narcolepsy and idiopathic hypersomnia, and can also be a normal phenomenon in certain circumstances (e.g., sleep deprivation). Some of these sleep disorders can be differentiated from narcolepsy or idiopathic hypersomnia by history. For instance, identification of a disruptive environmental feature during sleep may lead one to the diagnosis of an environmental sleep disorder. A history of sleeping less than expected from age-adjusted normative data or having a sleep period that is delayed, advanced, or irregular would suggest behaviorally induced, insufficient sleep syndrome or a circadian rhythm disorder, respectively. Psychiatric disorders (e.g., depression or substance abuse) can also be responsible for excessive sleepiness and are identifiable on history. A description of normal sleep between episodes of hypersomnia can suggest a diagnosis of recurrent hypersomnia.

Other disorders that cause excessive sleepiness cannot always be identified by history alone and require additional studies to differentiate them from narcolepsy and idiopathic hypersomnia. A polysomnogram will help identify sleep disordered breathing in a patient. Imaging studies may discover the presence of a brain tumor or stroke (although other findings on exam are also usually present). Blood work or CSF analysis can help identify metabolic abnormalities or encephalitis as a cause of the sleepiness. There was a case report by Maestri et al. [49] on a patient that was diagnosed with idiopathic hypersomnia but after further evaluation was found to have an insulinoma. After management of the insulinoma, his symptoms of excessive sleepiness resolved. Another report by Shinno et al. [50] identified a patient with idiopathic hypersomnia who was subsequently found to have subclinical hypothyroidism; after management with levothyroxine his sleepiness improved.

History and additional laboratory studies are also useful in ruling out disorders that can mimic cataplexy. Transient weakness episodes can represent transient ischemic attacks (TIAs) if there is no history of an association with emotion or if there is a history of vascular risk factors and/or stroke. Seizures, syncope, and brainstem or diencephalic tumors can look like cataplexy; a positive EEG may suggest seizures; imaging studies can help identify tumors; and a history of loss of consciousness may help differentiate syncope or seizures from cataplexy.

## ***Head Trauma and Excessive Sleepiness***

Sleep disturbances, including excessive sleepiness, can occur as a result of traumatic brain injury (TBI); accordingly, TBI should be considered in the differential diagnosis of excessive sleepiness. Some researchers contend that the excessive sleepiness is due to the increased prevalence of obstructive sleep apnea and periodic limb movement disorder that is seen in TBI patients [51]. In addition, changes in nocturnal sleep pattern seen in TBI patients are similar to those of depressed patients, namely, increased nighttime awakenings and longer sleep onset latency [52]. It is speculated that the sleepiness is due in part to this disturbed nocturnal sleep and that treatment of concomitant mood disorders may improve the sleepiness in the TBI patients; however, further research needs to be done in this area.

Hypothalamic damage, not necessarily visible on imaging studies, may be responsible for the excessive sleepiness that is seen in many TBI patients. The ICSD-2 classified this group of TBI patients under two separate categories: narcolepsy due to a medical condition and hypersomnia due to a medical condition (previously referred to as posttraumatic hypersomnia). A 2007 study found that the CSF hypocretin-1 levels were decreased in these TBI patients, and a follow-up study in 2009 demonstrated the number of hypocretin neurons in the hypothalamus was significantly reduced [53, 54]. The loss of hypocretin may be the etiology underlying TBI associated with narcolepsy and possibly posttraumatic hypersomnia.

There is limited data on the epidemiology of excessive sleepiness in TBI patients. In a 2001 study by Masel et al. [51], excessive sleepiness was identified in about 46% (33 out of 71) of brain injury patients. These patients were found to have either narcolepsy, posttraumatic hypersomnia, sleep apnea, or other sleep disorders that were responsible for the sleepiness. In another study, 55% (282 out of 514) of TBI patients were identified as having sleepiness; however, the etiology of the sleepiness was not investigated [55]. More recently, a study found subjective sleepiness to be common in a sample of 51 TBI patients [56]. In addition, Castriotta et al. [57] reported on a study population of 57 TBI patients of which 21% (12) demonstrated objective EDS on MSLT studies, 3% (2) had posttraumatic hypersomnia, 5% (3) had narcolepsy, 23% (13) had obstructive sleep apnea, and 7% (4) had periodic limb movements during sleep. Some studies suggest that the severity of the sleepiness correlates with the severity of the TBI [55, 58]; however, other studies contradict this finding [53, 59].

## **Treatment**

There is no known cure for either narcolepsy or idiopathic hypersomnia; however, with respect to idiopathic hypersomnia, there are reports of spontaneous remission [22]. For those with persistent disease, treatment is targeted at symptom management. Even with optimum management, the EDS in narcolepsy and idiopathic hypersomnia patients, and the cataplexy in narcolepsy patients, are seldom completely controlled.

## ***Nonpharmacologic Management***

Nonpharmacologic management should be initiated in all patients. Patient education is an important component of any treatment plan. Good sleep habits with avoidance of sleep deprivation and/or irregular sleep patterns should be emphasized. In narcolepsy patients, the scheduling of short naps (15–20 min) 2–3 times/day can help control EDS and improve alertness, but this is impractical in many settings. Napping, in contrast, is not recommended for management of sleepiness in patients with idiopathic hypersomnia as it usually does not help. Patients and family members should also be warned about the potential dangers of sleepiness relative to driving and/or in other hazardous settings. Typically, lifestyle changes alone are not enough to adequately control the symptoms of either narcolepsy or idiopathic hypersomnia; most patients require lifelong medication.

## ***Pharmacologic Management of Symptoms Common to Both Narcolepsy and Idiopathic Hypersomnia***

Pharmacological management of EDS, with a few exceptions, is similar in both narcolepsy and idiopathic hypersomnia; however, it should be noted that randomized, double-blind, placebo-controlled clinical trials have not been done on idiopathic hypersomnia patients. Stimulants, such as methylphenidate or dextroamphetamine, have previously been used as first-line therapy, but more recently modafinil and armodafinil have become the first-line treatment for most patients [60, 61]. Most clinical studies of stimulant medications report objective improvements in sleepiness in 65–85% of subjects.

Common adverse effects associated with stimulants include nervousness, headaches, irritability, tremor, insomnia, anorexia, gastrointestinal upset, and cardiovascular stimulation [62]. The development of drug tolerance or addiction can also occur; however, this risk is thought to be similar to other patient groups.

Modafinil is generally well tolerated, with headache and nausea being the most common side effects. Armodafinil is the long acting dextro-enantiomer component of racemic modafinil, which has equal amounts of *S*- and *R*-modafinil. It has a similar therapeutic and side effect profile to racemic modafinil, but with the advantage of having a longer elimination half-life ( $t_{1/2}$ ) (3–4 h for *S*-modafinil vs. 10–15 h for armodafinil) [63]. Although comparative studies have not been done in narcolepsy or idiopathic hypersomnia, armodafinil has been shown to be effective and produce longer wakefulness than racemic modafinil in patients with sleepiness due to acute sleep loss [64].

Sodium oxybate, the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous substance in the brain, is an effective medication in the treatment of daytime sleepiness in narcolepsy [60, 65]. It has not been systematically studied in patients with idiopathic hypersomnia. Sodium oxybate's adverse effects include nausea (19%),

dizziness (18% incidence), headache (18%), nasopharyngitis (6%), somnolence (6%), vomiting (8%), and urinary incontinence (6%) with most described as mild or moderate in severity. Dizziness, nausea, vomiting, and enuresis may be dose related [66].

Currently, sodium oxybate, amphetamines, methylphenidate, modafinil, and armodafinil are the only medications FDA approved in the United States for the treatment of narcolepsy. Other medications have been reported to have beneficial results, but little data is available [67]. All medications are used “off-label” for the management of excessive sleepiness due to idiopathic hypersomnia.

## *Pharmacologic Management of Symptoms Specific to Narcolepsy*

### **Cataplexy**

Although treatment of sleepiness can have a mild beneficial effect on cataplexy, most wake-promoting agents/stimulants do not provide sufficient relief from cataplexy. Most medications used for the treatment of cataplexy have REM sleep suppressant properties and/or increase aminergic (esp. by blocking the norepinephrine (NE) transporter) activity [68]. Tricyclic antidepressants (TCAs), serotonin reuptake inhibitors, and NE reuptake inhibitors have demonstrated benefit in animal studies (which is believed to be a function of the NE reuptake inhibition). Sodium oxybate is highly efficacious for the treatment of cataplexy in narcolepsy and is currently the only FDA approved medication for its management.

Several small open-label studies and several decades of use have demonstrated that the TCAs desmethylinipramine, protriptyline, imipramine, and desipramine have beneficial anticataplectic effects [69]; however, clomipramine remains the most widely used. Adverse events commonly associated with TCA therapy include nausea, anorexia, dry mouth, urinary retention, and tachycardia. Men may encounter decreased libido, impotency, or delayed ejaculation. An unusual property of TCAs is the rebound cataplexy phenomenon that occurs upon abrupt discontinuation of TCA therapy. When severe, this is known as status cataplecticus and can be disabling for several days [70].

Similar to TCAs, the SSRIs including fluvoxamine, zimeldine, femoxetine, paroxetine, and fluoxetine have all demonstrated anticataplectic activity; however, fluoxetine appears to be the most commonly used of the SSRIs for the treatment of cataplexy [71]. As a class, the SSRIs are generally less efficacious than TCAs; however, they have a better safety profile and are better tolerated than the older antidepressants. Reported adverse events include headache, nausea, weight gain, dry mouth, and delayed ejaculation [71]. Other antidepressant medications have also been found to have some anticataplectic activity; these include monamine oxidase inhibitors such as phenelzine and selegiline as well as other atypical antidepressants with pronounced NE reuptake inhibition, such as venlafaxine and atomoxetine.

## Fragmented Nocturnal Sleep

As mentioned earlier, sodium oxybate taken at bedtime and again during the night increases slow wave sleep, decreases light sleep (stage N1 sleep), and decreases the number of arousals. REM sleep is initially increased, but then decreases after increasing dose and duration of therapy [72].

Other medications have also been tried in the management of the fragmented sleep of narcoleptics. A study evaluating 0.25 mg of triazolam taken at bedtime showed improved sleep efficiency and overall sleep quality, but had no beneficial effect on daytime sleepiness [73]. Other medications such as zolpidem, eszopiclone, or clonazepam have been used with varying success in some patients (personal experience and conversations with other sleep medicine physicians). For symptoms of sleep paralysis and hypnagogic hallucinations, TCAs, other REM suppressant medications, and sodium oxybate have been successful.

## Conclusion

Narcolepsy and idiopathic hypersomnia are primary central hypersomnias characterized by persistent EDS. Whereas cataplexy is pathognomic for narcolepsy, there is no pathognomic symptom for idiopathic hypersomnia. Narcolepsy is currently believed to be due to a deficiency in hypocretin-producing neurons in the lateral hypothalamus, possibly as a result of an autoimmune disorder. The pathophysiology of idiopathic hypersomnia is currently unknown. The diagnosis is made by the presence of appropriate clinical symptoms and confirmation by polysomnography followed by an MSLT. The MSLT typically shows a short sleep latency ( $\leq 8$  min for narcolepsy and  $< 8$  min for idiopathic hypersomnia) with two or more sleep onset REM periods in narcolepsy patients vs. less than two sleep onset REM periods in idiopathic hypersomnia patients. In patients with cataplexy, CSF hypocretin levels are typically  $\leq 110$  pg/mL, but CSF histamine levels are reduced in both disorders. There are both nonpharmacologic and symptom directed pharmacologic (e.g., CNS stimulants, modafinil, sodium oxybate, certain antidepressants) treatments that usually are used together for optimal management of excessive sleepiness. Pharmacologic management for the cataplexy of narcolepsy includes medications with prominent NE reuptake inhibition and sodium oxybate.

## Summary of Keypoints

- Narcolepsy is a syndrome consisting of EDS, cataplexy, sleep paralysis, and hypnagogic hallucinations. Additional features include automatic behaviors and fragmented or disrupted nighttime sleep.
- Classic narcolepsy symptoms are difficult to identify in children as sleepiness may manifest as inattentiveness, lack of energy, behavioral problems, or decreased performance.

- Cataplexy is the most specific symptom of narcolepsy consisting of an abrupt, bilateral loss of skeletal muscle tone, triggered by sudden emotion such as laughter. Cataplexy is seen in 60–90% of patients with narcolepsy.
- Poor nighttime sleep is also common in narcolepsy, due to a dysfunction of central sleep regulation which causes frequent transitions between sleep and wakefulness throughout the entire 24-h cycle.
- Most cases of narcolepsy with cataplexy are associated with loss of hypocretin-containing hypothalamic neurons; cases of narcolepsy without cataplexy may be caused by a partial loss of these neurons.
- Sleep disturbances, including excessive sleepiness, may occur following TBI. It is important to consider TBI among the causes of EDS.
- Appropriate sleep hygiene is critically important in patients with narcolepsy or idiopathic hypersomnia. Short naps (15–20 min) 2–3 times/day can help control sleepiness in narcolepsy and improve alertness. However, scheduled naps are not recommended in idiopathic hypersomnia.
- Stimulants are the mainstay of management of daytime sleepiness in patients with narcolepsy or idiopathic hypersomnia. Most clinical studies of stimulant medications report objective improvements in sleepiness in 65–85% of subjects.

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# Chapter 17

## Parasomnias

Hrayr Attarian

### Introduction

There appears to be a lot of confusion in the medical community about what constitutes a parasomnia and how prevalent these conditions are. In the past, any sleep disorder that was not breathing related or did not present with prominent insomnia or daytime sleepiness was called a parasomnia. The International Classification of Sleep Disorders second edition (ICSD 2) restructured the different sleep disorders into pathophysiologically based categories. According to the ICSD 2, parasomnias are undesirable physical or experiential events that occur in and around sleep. It lists 16 parasomnias divided into three categories: NREM parasomnias or disorders of arousal, REM parasomnias, and other parasomnias.

### NREM Parasomnias or Disorders of Arousal

#### *Confusional Arousal*

##### Definition

Confusional arousal is a condition of partial or incomplete awakening usually out of slow wave or stage N3 sleep. The arousal is associated with slow mentation, relative unresponsiveness to the environment, occasional complex behaviors, and partial or total amnesia for the event. There is no autonomic hyperactivity as in sleep terrors and no wandering as in sleepwalking.

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## Clinical Symptomatology

Confusional episodes result from incomplete arousals during the first third of the major sleep period. They are characterized by complex and inappropriate behaviors, nonsense vocalizations, and unintelligible utterances. They rarely leave the bed and they do not exhibit signs of autonomic hyperactivity seen in sleep terrors. There is, however, potential for violence if the patient is forcibly aroused. External stimuli that cause sudden awakenings can lead to confusional arousals in the first 2–3 h of sleep. Events generally last minutes to hours and generally the more the external stimulation the longer they seem to last. There is memory impairment for the event in over half of subjects with confusional arousals [1]. A variant of confusional arousal happens with morning awakenings especially in people with primary hypersomnias or sleep deprivation. This is sometimes called “sleep drunkenness” or in French “*Ivresse du Sommeil*” and is characterized by clumsiness and mental cloudiness. Sleep deprivation can also lead to confusional arousals out of prolonged daytime naps as well.

## Etiology

There are no known etiological factors other than age as it is much more prevalent in children than adults. There are, however, precipitating factors such as use of central nervous system (CNS) depressant medications, sleep deprivation, exposure to alcohol, and certain metabolic conditions that can affect the CNS.

## Pathophysiology

Confusional arousals are manifestations of incomplete arousal from N3 sleep. Impairment in cognitive function and delayed responsiveness occurs in healthy sleepers as well if they are awakened from slow wave N3 sleep. Electrophysiological recordings during confusional arousals have demonstrated the coexistence of the hallmarks of different sleep stages within a single epoch.

There may be arousal in the limbic system with persistence of slow wave activity in the associative cortical areas responsible for higher cognitive functions [2].

## Epidemiology

The prevalence ranges from 2.9% in adults to 17.3% in children without gender predilection [3].

## Diagnostic Workup

Often history or a home video of the event is enough to make the diagnosis but in atypical cases video EEG monitoring may be required to rule out nocturnal seizures. Sometimes a PSG with extra EEG leads can be sufficient if an event occurs or one is precipitated by forced arousal from N3 sleep.

## Treatment

Reassurance in children with confusional arousals is first-line treatment as they often “outgrow” them with age [4]. Anticipatory or scheduled awakening is a behavioral technique used to prevent confusional arousals. Because the occurrence of these events is very often time-locked to the first third of the night awakening of the child, 15–20 min prior to the usual time of occurrence may alter the sleep state and therefore abort the event. During the scheduled awakening, the parent should comfort the child [3]. When confusional arousals become frequent and intractable the possibility of comorbid sleep disordered breathing or, to a lesser extent, sleep-related movement disorder should be explored. Treating these underlying conditions often eliminates the confusional arousal [5].

During a confusional arousal, efforts to curtail the behavior may lead to aggression because of the physical proximity and provocation and therefore should be avoided [6]. The episode should simply be allowed to run itself out, unless there is an attempt to leave the bed [7]. There is no specific pharmacological management for confusional arousals and often none is needed [7]. Anecdotal evidence suggests, however, that some tricyclic antidepressants such as imipramine and clomipramine might benefit some patients as can low dose clonazepam [7]. Patients should avoid any known precipitating factors, such as sleep deprivation, shift work, or CNS depressants especially alcohol [8].

## *Sleepwalking or Somnambulism*

### Definition

Sleepwalking is a disorder of arousal characterized by complex purposeless tasks and wandering episodes of variable duration, with memory impairment for the event.

### Clinical Symptomatology

Sleepwalking usually occurs in the first 2–3 h of the major sleep period, when N3 sleep is the most prevalent stage. Sleepwalkers perform movements of varying complexity that range from just changing positions on bed to actually getting out of bed and walking to cooking, eating, and even driving a car. All movements, however, are clumsy and purposeless. Even when the event is associated with talking, speech is slow and poorly reactive. They do though sometimes respond to commands of returning to bed. They may carry on incoherent conversations but they never scream, yell, or otherwise make any alarming vocalizations or show signs of autonomic hyperactivity. The onset of the event is usually abrupt and the subjects are usually indifferent to their environment, have a blank facial expression, and have little or no awareness of their surroundings. They may react minimally but usually

are unresponsive and difficult to arouse despite the fact that they appear awake although disoriented and confused. Episodes usually begin abruptly, and patients show a blank expression, indifferent to the environment with a low level of awareness and reactivity. Sleepwalking has potential forensic implications because of rare injurious behaviors including homicides that have occurred [9]. Violence often occurs when attempts to wake the sleepwalker lead only to partial arousal. Amnesia for the event is quite common unless the person was fully awakened during the event. There have been, however, reports of some elaborate dream-like experiences.

## **Etiology**

Genetics seem to play a big role in sleepwalking as it often runs in families together with other NREM parasomnias. Sleepwalking occurs with higher concordance in monozygotic than dizygotic twins [10] and there is an association between sleepwalking and HLA-DQB1\*05 subtype [11]. Sleepwalking occurs commonly in children aged 5–16 years, with a peak at age 10. CNS maturational factors may play a role in the termination of episodes by late adolescence. Because of its strong association with migraines but not other types of headaches [12] a dysfunction of the serotonergic system has also been implicated as a contributing factor [13]. Adults who present with sleepwalking have often had history of sleepwalking in childhood or never stopped sleepwalking in late adolescence, although rare adult onset has been reported. It is very important to recognize in clinical practice that drugs both prescribed and recreational can cause sleepwalking and although zolpidem and other sedative hypnotics have been recently implicated more often than other medications the potential exists with any CNS active agents. Even though sleepwalking tends to be more prevalent with psychosocial stressors, contrary to popular lore, sleepwalking in adulthood is not a sign of psychiatric illness [14].

## **Pathophysiology**

As with the other NREM parasomnias, sleepwalking tends to arise most of the time from stage N3 sleep, but may occasionally arise out of N2 sleep. Although no direct evidence exists the current thinking based on robust circumstantial data is that sleepwalking is due to an arousing stimulus leading to incomplete cortical activation. Sleepwalkers tend to have NREM sleep instability with inability to maintain consolidated N3 sleep [15]. Single Photon Emission Computerized Tomography (SPECT) studies in sleepwalkers have shown activation of the thalamocingulate tracks (responsible for motor activity) with continued quiescence of thalamocortical tracks (responsible for wakefulness). Therefore, during sleepwalking the mind is sleep while the motor systems are awake [16].

## Epidemiology

Prevalence of sleepwalking varies from 4% in adults to 17% in children under the age of 13 [17].

## Diagnostic Workup

In most typical cases, history alone is sufficient to make a diagnosis but in atypical presentations, especially in adults, nocturnal seizures need to be ruled out that is why a couple of nights of video EEG monitoring is usually sufficient to make a diagnosis [18]. If other underlying sleep disorders are suspected then a PSG with additional EEG electrodes may be helpful [19]. In addition, sleep depriving the patient the night before may increase the yield of capturing an event during the PSG [20, 21].

## Treatment

Because of absence of randomized trial data on the efficacy of pharmacological measures the first-line treatment for sleep walking is supportive. This includes avoiding sleep deprivation and treating other apparent predisposing factors (e.g., sleep disorders), addressing triggering factors (e.g., environmental stresses and intake of alcohol and other drugs) and creating a safe environment for the sleepwalker (removing objects they can bump into, locking windows, etc.), quietly guiding him or her back to bed if necessary and reassuring that underlying psychiatric illness is not the cause of the sleepwalking [22]. With pediatric cases parents should also be reassured, once other conditions such as seizure disorders, have been ruled out, that most affected children usually outgrow the condition by late adolescence, or sooner [3]. In addition, anticipatory or scheduled awakening, described earlier, can also be utilized to prevent sleepwalking [23, 24]. Other nonpharmacological methods of treatment include psychotherapy and stress management [7], including hypnosis [25] (see Table 17.1 for a detailed list). The evidence for these methods is only based on anecdotal data and case reports and the only randomized, blind trial (only 11 participants) that compared active hypnosis to suggestion hypnotherapy with crossover did not show any additional benefit with the active therapy [26].

If the sleepwalking is putting the patient and the family at risk for injury or if the events are frequent and disruptive to both families' and patients' sleep then pharmacological management is recommended.

Several case reports and anecdotal data have shown that patients respond to benzodiazepines such as diazepam 2–5 mg [25] although in a small (five subjects) double blind crossover study, the only one of its kind, diazepam was not superior to placebo because all five patients significantly improved [27]. Clonazepam at 0.5–2 mg is the best documented medication for sleepwalking in several case series [28, 29].

**Table 17.1** Summary of therapies for NREM parasomnias

Parasomnia	Nonpharmacological treatment	Pharmacological treatment
Confusional arousals	Scheduled awakening	Imipramine/clomipramine Clonazepam
Sleepwalking	Scheduled awakening	Diazepam (although small randomized trial did not show benefit)
	Stress management	Clonazepam/ Triazolam/flurazepam
	hypnosis (although small randomized trial did not show benefit)	Imipramine Melatonin Paroxetine
Sleep terrors	Scheduled awakening	Trazodone
	hypnosis	Paroxetine
	Relaxation therapy	Diazepam/clonazepam Hydroxytryptophan Imipramine/clomipramine

Other benzodiazepines that have been shown effective include triazolam 0.25 mg at bedtime [30] and flurazepam [31]. Imipramine 20–100 mg at bedtime is effective for many patients [25, 32, 33]. Lastly, paroxetine is reported effective in isolated cases [34, 35]. When patients with initially frequent sleepwalking are totally controlled for 4–6 months, nightly use of medication should be followed by gradual withdrawal within a year, and resumption if symptoms return [25].

Some case studies have suggested that melatonin therapy, at 5 mg, half an hour before bedtime, may be helpful for patients with sleep walking [36].

*Sleep Terror or Pavor Nocturnus*

**Definition**

Sleep terror is a NREM parasomnia characterized by an explosive onset, autonomic hyperactivity, and a “blood curdling” scream.

**Clinical Symptomatology**

Sleep terrors usually consist of an abrupt arousal from stage N3 sleep with a sudden scream and incoherent verbalizations often within the first hour of the major sleep period. The individual then enters a state characterized by autonomic hyperactivity [4] and behavioral manifestations of intense fear and sometimes an apparent desire to escape. Episodes are usually short lasting under 5 min except on rare occasions can be as long as 20 min, and not occurring more than once a night. Patients do not usually leave the bed although jumping out of bed and running through the house have been reported. Patients quickly return to sleep and there is usually amnesia for

the event the next day or the recollection is limited to a single frightening image or situation. In rare, severe cases, injury to the patient or people trying to restrain him or her may occur.

## **Etiology**

As with sleepwalking, genetic factors play a role in the etiology of sleep terrors with increased prevalence among subjects with family history of sleep terror or any of the other two NREM parasomnias. Twin studies also support the role of genetics [37]. Sleep terrors have also been reported in posttraumatic stress disorder (PTSD) [38], in children with OSA [5], and patients with certain brain lesions [39].

## **Pathophysiology**

The exact pathogenesis remains unknown but as with all disorders of arousal sleep terrors tend to rise out of N3 sleep and disorder of arousal mechanisms with fragmented N3 sleep has been implicated as one causative factor [40, 41].

## **Epidemiology**

Prevalence of sleep terror also varies with age from 1% in the elderly to 6.5% in children [8].

## **Diagnostic Workup**

History alone is usually sufficient to make the diagnosis of typical sleep terrors but as with other parasomnias nocturnal seizures need to be ruled out with video EEG monitoring in atypical presentations and if other sleep disorders such as OSA is suspected a PSG also is recommended.

## **Treatment**

Reassurance is often enough in young children with infrequent spells of sleep terrors because they tend to outgrow it by late adolescence [4]. It is, however, very important to have safety measures in place to avoid injury [4]. Any attempt at interrupting the episode is discouraged because it will frighten the person experiencing the sleep terror and may lead to violence [42]. It is preferable to wait until the spell is over and then guide the person gently back to bed [42].

The bedroom environment should be made as safe as possible to minimize the risk of injury. These include locating the patient's bedroom on the ground floor,



providing special bolts for windows and doors, removing obstructions in the bedroom, and installing alarms on outside doors [42]. In children, anticipatory or scheduled awakening, described earlier, can also be utilized to prevent sleep terrors [23, 24].

The patient should be counseled to avoid sleep deprivation and other precipitants, such as drugs and alcohol [7]. Attempts should be made to alleviate whatever stress may be going on in the patient's environment and to ensure that the patient (especially a child) is getting adequate rest [43].

If the behaviors are dangerous to person or property or extremely disruptive to family members then there are both behavioral and pharmacological methods to treat sleep terrors [7].

Behavioral methods include psychotherapy [44], relaxation therapy [45], and autogenic training or hypnosis [46].

Pharmacological interventions include benzodiazepines such as diazepam 5–10 mg [47] or clonazepam 0.5–2 mg [29] and tricyclics such as imipramine [48] or clomipramine [49] may be beneficial. Other medications that have anecdotal evidence for their efficacy are trazodone and paroxetine [50], melatonin 5 mg in children with pervasive developmental disorders [36, 51], and lastly L-5-hydroxytryptophan, a precursor of serotonin, (2 mg/Kg at bedtime) has been proposed as highly effective in reducing the number of sleep terror episodes [52].

## **REM Parasomnias**

### ***REM Sleep Behavior Disorder***

#### **Definition**

Sleep behavior disorder (RBD) is characterized by the absence of atonia in REM sleep resulting in dream enacting behavior that can lead to injury to self and bed partner.

#### **Clinical Symptomatology**

The most common presenting symptom is the violent and dramatic activity in sleep that can potentially lead to injury. This activity can take the form of loud vocalizations like talking, yelling, or swearing, and it can cause the patient to grab, jump, punch, and kick and even run out of bed. Rarely elaborate nonviolent behaviors can also occur, especially among adolescents and women [53]. Obviously injuries can be quite common and range from bruises to multiple fractures and can involve both the person and their bed partner. The violent behaviors and dream content associated with RBD are usually completely out of character for the patient and there is no increased daytime aggressiveness [54–56]. There is always memory for

the event, which tends to be short with no confusion upon awakening and clear dream mentation. Events tend to happen in the middle or latter third of the night and rarely arise out of naps. They can occur anywhere from several a night to one every few weeks and the patients may have had a prodrome lasting for several years of frequent sleep talking, periodic limb movements, and tooth grinding.

## **Etiology**

Acute and transient RBD can develop in response to medications especially SSRIs [57, 58]. A clear etiology of chronic RBD has not been discovered but a clear association between RBD and degenerative neurological illnesses such as synucleinopathies (Parkinson disease, dementia with Lewy Body disease, and multisystem atrophy) has been clearly established. Often the RBD precedes the other symptoms of the neurological illness by up to five decades [59]. Another condition closely associated with RBD is narcolepsy; over 50% of patients with narcolepsy complain of dream enacting behavior [60].

## **Pathophysiology**

The most likely pathophysiology of RBD is a dysfunction in dopaminergic systems, particularly in the striatum, but also involving the pons and portions of the frontal lobe. The evidence for this comes mainly from functional neuroimaging [61–64].

## **Epidemiology**

The estimated prevalence is 0.38% in the general population and 0.5% in elderly men [65]. RBD is most common in men older than 50 but it may start at any age. Women, younger adults, and children can also present with it [53, 66–69]. Serum sex hormone abnormalities do not account for the male predominance [70].

## **Diagnostic Workup**

History of dream enacting behavior and PSG evidence of excessive chin EMG tone seen on a single night of recording is sufficient to establish the diagnosis even if the person does not have one of their episodes in the lab [71].

## **Treatment**

RBD-like symptoms can occur in untreated Obstructive Sleep Apnea Syndrome (OSAS) and treating the underlying sleep-related breathing disorder will generally

control the RBD [72, 73]. Certain antidepressants (SSRIs, venlafaxine, and related medications) can also precipitate RBD and generally treatment involves stopping the offending medications [57, 58].

Under all other circumstances RBD must be treated with medications. Creating a safe environment might help prevent injury but is not a stand-alone treatment. Although no randomized double blind trials exist [74] two agents shown to be definitely beneficial are clonazepam and melatonin.

Over 22 published papers and a total of 339 patients, clonazepam, at doses of 0.5–2 mg, taken 30 min before bed, was shown effective in controlling RBD symptoms completely in 251 (74%) and partially in 57 (17%) [75]. In addition, clonazepam has been known to normalize chin EMG activity on PSG in some patients with RBD [76]. Clonazepam should be used with caution in patients with dementia, gait disorders, or OSA [75].

Melatonin at doses of 3–12 mg (over 6 studies and 31 out of 38 subjects responding) has also been known to significantly improve but not necessarily completely resolve symptoms of RBD. It also has the added advantage of a favorable side effect profile [75]. A recent case report of a patient with the parasomnia overlap variant described complete resolution of RBD and sleep walking with melatonin but not with clonazepam [77]. No data is available on their combined use.

There are also a host of medications that have shown questionable benefit in RBD (see Table 17.2 for a detailed list). These include donepezil at 10–15 mg dose; rivastigmine 9–12 mg; pramipexole at 0.5–1.5 mg; levodopa at variable dosing; paroxetine at 10–40 mg; zopiclone 3.75–7.5 mg; temazepam, triazolam, and alprazolam at variable doses; the herbal supplement Yi-Gan San at 7.5 mg; sodium oxybate and clozapine at unknown doses; low dose desipramine (50 mg); and carbamazepine 300–1,500 mg a day [75]. Donepezil, 10–15 mg, has shown improvement in a small case series of idiopathic RBD patients [78] but failed to show significant improvement in RBD patients comorbid with neurodegenerative conditions [79, 80]. Rivastigmine, 9–12 mg, has only been studied in patients with RBD and Lewy Body Dementia and has shown modest if any benefit [81, 82]. Pramipexole 0.5–1.5 mg has shown to be somewhat beneficial in idiopathic RBD [83] but not RBD with parkinsonian syndromes [84] and levodopa at 100 mg, in patients with parkinsonism has improved but not resolved RBD symptoms [85]. Despite the ample data available on the negative effect of SSRIs on RBD there is a single case report where paroxetine [86] improved both clinical symptoms and PSG signs of idiopathic RBD.

Therefore, the AASM standards of practice committee recommend the following:

Pramipexole may be considered to treat RBD but efficacy studies have shown contradictory results. There is little evidence to support the use of paroxetine or L-DOPA to treat RBD, and some studies have suggested that these drugs may actually induce or exacerbate RBD. There are limited data regarding the efficacy of acetylcholinesterase inhibitors, but they may be considered to treat RBD in patients with a concomitant synucleinopathy [7].

The other medications listed earlier may be used for RBD but the data is only a few case reports, therefore evidence to support their use is very limited [75].

**Table 17.2** Summary of therapies for REM parasomnias

Parasomnia	Nonpharmacological treatment	Pharmacological treatment
RBD	none	Melatonin: Level B evidence Clonazepam: Level B evidence Zopiclone, benzodiazepines other than clonazepam, Yi-Gan San, desipramine, clozapine, carbamazepine, and sodium oxybate: Level C evidence Rivastigmine and donepezil Level C evidence only in the setting of synucleinopathies Pramipexole, levodopa, and paroxetine (controversial evidence)
Parasomnia Overlap Syndrome		Clonazepam: Level B evidence
Isolated Sleep Paralysis	none	Tricyclic antidepressants: Level B evidence SSRIs: Level C evidence Magnetic stimulation (one case report)
Nightmares	Image Rehearsal Therapy: Level A evidence Systematic Desensitization and progressive deep muscle Relaxation: Level B evidence Exposure, relaxation, and rescripting therapy (ERRT); sleep dynamic therapy; hypnosis; eye-movement desensitization and reprocessing (EMDR); and the Testimony Method: Level C	Prazosin: Level A evidence (only in PTSD) Tricyclic antidepressants, phenelzine, fluvoxamine, trazodone, olanzapine, topiramate, gabapentin, cannabinoid, low dose cortisol, cyproheptadine triazolam and nitrazepam: Level C Clonidine: Level C evidence (only in PTSD)

### *Parasomnia Overlap Syndrome/Status Dissociates*

These are two subtypes of RBD with an unknown prevalence and tend to occur in a variety of neurological and psychiatric conditions. The first is characterized by the co-occurrence of both RBD and a NREM parasomnia usually sleep walking or confusional arousal and the latter is characterized by the complete breakdown of all interstate boundaries resulting in no identifiable sleep/wake stages [87]. For all practical purposes, their diagnostic workup and treatment is the same as that of RBD.

## ***Isolated Recurrent Sleep Paralysis***

### **Definition**

This is a condition characterized by a pathological dissociation between level of alertness and the generalized muscle atonia typical of REM sleep leading to the feeling of being paralyzed but entirely alert [88].

### **Clinical Symptomatology**

Isolated paralysis most often occurs when awakening (postdormital or hypnopompic type) whereas the familial and the type associated with narcolepsy tend to occur more while falling asleep (predormital or hypnagogic) [89]. Both types, however, can occur in all three conditions.

The person is unable to move limbs, facial muscles, or vocalize. Although there is a subjective sense of shortness of breath, respiratory muscles are spared. The person experiencing it is always fully awake and can easily recall the event afterwards. The episode lasts seconds to minutes (average duration 4 min) and usually resolves spontaneously but may be aborted by sensory, usually tactile, stimulation [89]. Intense anxiety is often a feature of the event and hallucinations can accompany sleep paralysis up to  $\frac{3}{4}$  of the time. Relapses can occur especially if one is lying in the supine position. Frequency of the episodes is also more in supine sleepers and those who experience it at the beginning and middle of the night rather than at the end of the night. Timing also affects severity of the anxiety with sleep onset episodes being more anxiety provoking. Usually sleep paralysis leaves no sequelae but on rare occasions, some weakness or numbness in the extremities may persist for a few minutes [90].

### **Etiology**

The etiology of isolated recurrent sleep paralysis is unknown.

### **Pathophysiology**

A dissociated state of mixed wake and REM sleep is the most likely cause of sleep paralysis [91]. This is most likely due to hyperactivity of the cholinergic systems in the brainstem as well as hypoactivity of the noradrenergic and serotonergic mechanisms.

### **Epidemiology**

The prevalence varied between 5 and 40% depending on frequency of the experience, age group, and type of questionnaires used [92–97].

## Diagnostic Workup

Polysomnography captures sleep onset REM periods and dissociated states of wake and REM if the events are frequent enough to be captured during a recording [98]. History alone may also be sufficient but the recently developed Unusual Sleep Experiences Questionnaire can also be of use [99].

## Treatment

Sleep deprivation can increase the frequency of sleep paralysis and can often precipitate an episode. Avoidance of sleep deprivation is highly recommended especially in cases of shift work and other related circadian problems such as jet lag, irregular sleep habits, etc [100]. In cases of isolated or familial sleep paralysis or with narcolepsy when episodes are quite frequent then pharmacological intervention is warranted. Medications that have shown to be effective by anecdotal reports include clomipramine 25–50 mg at bedtime; [101] imipramine at a dose of 25–50 mg [102]; protriptyline 2–10 mg; fluoxetine 10–30 mg; viloxazine 25–50 mg; and femoxetine 100–150 mg [103]. Their proposed mechanism of action is through REM suppression [104]. A single case report of a patient with multiple sclerosis and frequent isolated sleep paralysis describes resolution of the paralysis with extracerebral weak electromagnetic field [105].

## Nightmares

### Definition

Nightmares are anxiety and fear provoking recurrent dreams.

### Clinical Symptomatology

The four cardinal criteria to diagnose nightmares are:

1. A sudden awakening from sleep with intense fear, anxiety, and a feeling of impending harm.
2. Immediate recall of frightening dream content.
3. Full alertness on awakening with little confusion or disorientation.
4. A delayed return to sleep, or the episode occurs in the last half of the night [88].

There usually is a lack of shortness of breath, autonomic hyperactivity, or motor behaviors.

## **Etiology**

Two theories of nightmare etiology exist. The first, and the more valid one, postulates that nightmares are simulations of threatening events and serve a rehearsal function important for survival [106]. The second, which requires further testing to prove its validity, states that nightmares reflect negative waking-life experiences [107].

A number of medical conditions are also associated with nightmares and these include: advanced cancer [108], hypoglycemia resulting from insulin treatment [109], psychiatric disorders [110] especially PTSD [111], drugs (propranolol, levodopa, memantine, donepezil, valsartan, fluoxetine, reserpine and withdrawal from alcohol, barbiturates and high dose tricyclic antidepressants) [112–115], OSA [116], Parkinson disease [117], and epilepsy [118].

## **Pathophysiology**

Pathophysiology of nightmares is poorly understood but it is most likely a combination of genetic and environmental factors.

## **Epidemiology**

The prevalence, depending on age, comorbid conditions, and frequency of occurrence, varies from 2 to 85% [119].

## **Diagnostic Workup**

History alone is usually sufficient to establish the diagnosis. Comorbid conditions may need to be ruled out.

## **Treatment**

Nonpharmacological methods of treatment verified by small randomized trials include cognitive behavioral therapy [120] specifically imagery rehearsal therapy a technique where subjects change the endings of their nightmares, while they are awake, by rehearsing the new, nonthreatening images associated with the changed dream [121], cognitive restructuring called “lucid dreaming treatment,” where the subject is taught to realize that they are dreaming and change the content of their nightmares [122] self-exposure therapy (controlled exposure to cues associated with the nightmares; a form of desensitization) [123] and hypnosis [124]. A combination of sleep hygiene and a few of the above mentioned techniques showed improvement in both the psychiatric symptoms and sleep disturbances in an open label trial with PTSD patients [125] as did a combination of dream rehearsal, lucid

dreaming, and relaxation techniques [126]. Another randomized, clinical trial of cognitive-behavioral treatment for chronic nightmares in adults also reported a significant decrease in the nightmares themselves and significant improvement of comorbid depression, PTSD, quality and quantity of sleep. Using cognitive-behavioral treatment as a first-line therapy for trauma-exposed individuals with chronic nightmares is supported by this and other studies [127].

The best studied and most effective pharmacological measure to treat nightmares with PTSD has been the centrally active  $\alpha_1$ -adrenergic antagonist prazosin at 1–4 mg a day. Several trials both open label and placebo controlled have shown significant improvement in nightmares and associated sleep disturbances [128–133].

One of the mainstays of pharmacological treatment in most parasomnias, clonazepam, has been shown ineffective in controlling nightmares and related sleep disturbances in PTSD patients [134] but two other benzodiazepines, 0.5 mg triazolam and 5 mg nitrazepam, have anecdotal evidence of efficacy [135]. No data is available as to its efficacy in non-PTSD chronic nightmare sufferers. Other medications that have shown some benefit include the antidepressants nefazodone (not to be used first line because of hepatotoxicity [135]) with dosages of 400–600 mg [136] and trazodone 50–200 mg [137]. Both appear effective for the treatment nightmares and associated insomnia in noncontrolled open label trials. Other antidepressants with anecdotal evidence supporting their efficacy in nightmares include phenelzine, fluvoxamine, imipramine, doxepin, and amitriptyline [135]. Other medications that have been used in open label trials and have been shown somewhat effective include clonidine 0.2–0.6 mg in divided doses [135], cyproheptadine 16–24 mg per night, and 10 mg per day of cortisol [135]. Two anticonvulsants also have shown significant improvement in the frequency of nightmares and associated sleep disturbances in open label trials. These are gabapentin 300–3,600 mg per day [138], and topiramate at 75 mg a day [139], so has the atypical antipsychotic olanzapine at 10–20 mg a day doses [140]. Most recently a synthetic cannabinoid has shown significant improvements in number and frequency of nightmares in an open label trial [141].

## Other Parasomnias

### *Sleep-Related Dissociative Disorder*

Sleep-related dissociative disorder is a relatively new parasomnia that appeared in 2005 in the ICSD-2. It is the nocturnal variant of the psychiatric conditions that are grouped together under dissociative disorders [88].

Very little is known about its etiology or pathogenesis except that most if not all patients who experience sleep-related dissociative disorder have history of extensive sexual or physical abuse very often beginning in childhood [142]. Although the clinical criteria and symptomatology are the same as that of daytime dissociative



disorders criteria include the diagnosis of a dissociative disorder based on DSM-IV-TR criteria, dissociative episodes can exclusively or primarily arise from the main sleep period [143].

Clinically dissociative episodes occur when the person is technically awake by EEG criteria. The timing is usually either while transitioning from wake to sleep or during awakenings out of the major sleep period [29].

Diagnosis is made using the same DSM IV TR criteria as dissociative disorders which are characterized by disruptions of aspects of consciousness, identity, memory, motor behavior, or environmental awareness [144]. When events are captured during a PSG preferably with a full head EEG montage the subject is usually awake by EEG criteria but are completely unaware of their own actions and surrounding but the behaviors can be so complex as to lead to injury to self or others. It is unclear whether the sleep-related dissociative disorder represents a different clinical entity or if it is a subtype of the dissociative disorders in general [144]. The prevalence is unknown and the only epidemiological study reported that 5.3% of a sample of 150 patients with sleep-related injury had sleep-related dissociative disorder [143].

## **Treatment**

Various forms of psychotherapy are the mainstay of treatment for this challenging disorder. The involvement of a highly trained psychotherapist is key to successful treatment. Cognitive-behavioral therapy, sensorimotor psychotherapy (a method that integrates sensorimotor processing with cognitive and emotional processing in the treatment of trauma) [145], posttraumatic disorder treatment, and clinical hypnosis are all known to help [146]. Expressive artwork and journal entries can be useful complements to therapy and safety planning is essential because of high risk of suicidal ideation with patients with dissociative disorders [4].

## ***Sleep Enuresis***

### **Definition**

Sleep enuresis is defined as sleep-related recurrent and involuntary urination or in laymen terms bedwetting.

### **Clinical Symptomatology**

Enuresis is categorized as monosymptomatic or nonmonosymptomatic and also as primary or secondary.

When enuresis occurs in the absence of any daytime urinary symptoms then it is classified as monosymptomatic. The nonmonosymptomatic type is more common

as the majority of children have enuresis also exhibit subtle daytime symptoms. Secondary enuresis is bedwetting that develops after at least 6 consecutive months of dryness. The clinical presentation of primary and secondary enuresis is otherwise similar [147].

## **Etiology**

The etiology of enuresis remains unknown. Risk factors and contributors include CNS immaturity, disorders of arousal, increased fluid intake, urinary problems both functional and structural, male gender, maternal smoking, mother's age less than 20 at the time of the child's birth, psychosocial stressors, and ADHD [148, 149].

## **Pathophysiology**

The pathogenesis of enuresis remains unknown but genetics plays a major role in its development as enuresis is more common in children born to enuretic parents than in the general population. The incidence is 77% when both parents were enuretic and 44% when one parent was enuretic. In addition, 70% of enuretic children have at least one other sibling who also wets the bed. The inheritance pattern appears to be autosomal dominant with markers on chromosomes 12, 13, and 22 [150]. Psychosocial stressors, medications, and CHF (in the elderly) play a role in enuresis [151] as well in addition to hormonal changes such as lack of the normal nighttime peak in antidiuretic hormone [152] and elevated mean arterial pressure [153].

## **Epidemiology**

Approximately, 4% of 8 year olds have enuresis twice a week, 80% of 2 year olds, 30% of 4 year olds, 18% of 5 year olds, 10% of 6 year olds, 8% of 8 year olds, 3–4% of 12 year olds, and 1% of 15 year olds have enuresis at least once a month [154–156] and 8% of 7–15 year olds bedwet at least once every 3 months [157]. A total of 75–80% of cases are primary and 20–25% are secondary. The primary to secondary ratio decreases with increasing age, with each type accounting for half the cases by early adolescence. The female to male ratio in preadolescents is 1/1.5.

## **Diagnostic Workup**

Should include comprehensive sleep and urological history, a careful physical exam and urinalysis. Ultrasonography, vesical sphincter electromyography, cystometry, and cystoscopy may be useful for some children who have daytime symptoms or are resistant to treatment. A PSG with or without extra EEG channels may be indicated if OSA or nocturnal epilepsy is suspected [147]

## Treatment

The treatment of sleep enuresis should start by ruling out, with a careful history and examination, and treating potential secondary causes of it. OSAS is a known cause of bedwetting [158] as are genitourinary and renal problems [159], seizures [160], Attention Deficit Disorder (ADD) [161], diabetes mellitus [162], certain medications (certain antipsychotics, valproate, selective serotonin reuptake inhibitors (SSRI) [163–166], hyperthyroidism [167], and psychological factors such as history of sexual abuse [168]. When the above have been ruled out then the treatments of enuresis fall under three major categories: behavioral therapy, alarm therapy (used primarily in children), and pharmacotherapy [147]. Behavioral therapy is supported by a wealth of clinical and anecdotal data but no randomized trials are available to validate its efficacy. Nevertheless, it has very few drawbacks and should be attempted as first line. It includes proper bowel regimen to avoid hard stools or constipation as this may cause or worsen enuresis [169], increasing fluid intake during the morning and early afternoon hours and limiting it during the evening and night time [170], encouraging the patient to avoid holding urine and to void at least once every 2 h [147, 170], and biofeedback to help relax the pelvic floor muscles [147, 171]. Alarm therapy has been shown to be efficacious in multiple randomized trials [172]. It involves using a moisture sensitive alarm that goes off and awakens the child at the moment of bed wetting. It improves the child's ability to wake up from sleep by using classical conditioning or avoidance conditioning [173]. In successful cases, enuresis is replaced by nocturia [174]. Response is seen in the first month and treatment is continued for up to 6 months. If there is no response during the first month then the therapy is considered a failure and is discontinued [147]. Pharmacological treatments do not constitute a cure and generally relapses occur once the patient has stopped the medication. The drugs that have randomized trial support for efficacy include anticholinergics (especially antimuscarinic agents), e.g., oxybutynin, DDAVP or desmopressin, tricyclic antidepressants for children [147] and for adults all the above plus verapamil (55% efficacy and well tolerated) [175] (see Table 17.3 for a detailed list). There are anecdotal reports of acupuncture [176], spinal blocks with opiates [177], and bladder transection surgery [178] being helpful in adults with enuresis but most of these reports are from 20 or more years ago. Desmopressin is used as first-line pharmacotherapy for children with enuresis at 200–600 µg tablets 1 h before bedtime. Its mechanism of action appears to be the reduction of nocturnal polyuria [147]. It has up to 48% efficacy [179–181] but has the risk of water intoxication that can lead to coma and seizures due to hyponatremia [182]. This is especially true with the nasal spray formulation, therefore the nasal spray is not recommended in children [183]. Postmarketing case report and Medline survey from 1972 to 2005 conducted by Robson and colleagues identified 151 cases of hyponatremia with desmopressin out of which 145 were with the nasal spray and only 6 with oral tablets [183]. Caution is also advised while adding this medication to others that may potentially reduce seizure threshold or worsen hyponatremia [183]. Both desmopressin nasal spray and tablets have been shown effective with a is recommended for adults with enuresis with a 31–54% efficacy

**Table 17.3** Summary of therapies for other parasomnias

Parasomnia	Nonpharmacological treatment	Pharmacological treatment
Sleep related dissociative disorder	Cognitive-behavioral therapy	None
Sleep enuresis	Behavior modifications (controlled trials)	DDAVP (controlled trials)
	Biofeedback (controlled trials)	Oxybutynin and tolterodine (controlled trials)
	Conditioning (controlled trials)	Tricyclic antidepressants (controlled trials)
	Alarm therapy (controlled trials)	Verapamil (controlled trials)
	Acupuncture (case report)	
	Spinal block (case report)	
Catathrenia	Bladder transection (case report)	
	CPAP	None
Exploding head Syndrome	None	Nifedipine (some anecdotal data)
		Clomipramine (some anecdotal data)
		Topiramate (one case report)
		Flunarizine (some anecdotal data)
Sleep-related hallucinations	None	None
SRED	None	Pramipexole (small controlled trial) Topiramate (controlled trial)

and side effects profile that was comparable with both formulations. Symptomatic hyponatremia was about 5% [184].

There are no monotherapy trials to look at the efficacy of anticholinergics in pediatric enuresis but there are two recent well-controlled trials of long-acting anticholinergics (oxybutynin 5 mg and tolterodine LA 2 mg) added to desmopressin in children who did not respond to desmopressin alone. The efficacy was 66–68% and the combination was well tolerated [185, 186]. Side effects include facial flushing, heat intolerance, constipation, dry mouth, blurred vision, and increased residual urine [147]. In adults, oxybutynin at 5 mg doses has been shown effective (70%) [175] and well tolerated as has tolterodine at 4 mg doses with 69% efficacy [187]. The mechanism of action of anticholinergics is reduction of detrusor overactivity and an increase in bladder capacity [147].

Third-line pharmacotherapy includes the tricyclic antidepressants whose mechanism of action in enuresis is unknown. There is, however, ample evidence for their efficacy [147]. In children they are third line primarily because of potential cardiac toxicity [188]. Imipramine, trimipramine, and other similar antidepressants have been found effective in 20% of study subjects [188]. The recommended dose usually is 25–75 mg of imipramine (or the equivalent dose in other antidepressants) at bedtime [147]. A novel noradrenaline-reuptake inhibitor, Reboxetine, although pharmacologically related to imipramine, does not have the same risk of cardiotoxicity

and is shown, in one small study, to control enuresis in 32% of study subjects as monotherapy and for an additional 27% when combined with desmopressin [189].

There are no randomized trials in adults looking at tricyclics for enuresis. Imipramine at 1 mg/kg dose at bedtime has the best anecdotal data supporting its use [190, 191]. There are case reports on amitriptyline [192] and maprotiline [193] being helpful in adults with enuresis as well.

## ***Sleep-Related Eating Disorder***

### **Definition**

Sleep-related eating disorder (SRED) is a parasomnia that is characterized by partial arousals from sleep followed by eating or drinking with poor or no memory of the event afterwards. [194]

### **Etiology**

The etiology of SRED remains unknown but there are a few contributing factors. A large proportion of SRED patients have some psychopathology, therefore depression has been proposed as a risk factor [195] but a large Japanese study with a cohort of 2,023 found no relationship between depression and SRED [196]. Hormonal changes, particularly in melatonin, leptin, and cortisol levels have also been described in SRED [197] especially in those with insomnia. Finally, SRED has been seen as a side effect of zolpidem ingestion especially at doses higher than 10 mg [198].

### **Pathophysiology**

Although the exact pathogenesis of SRED is unknown it can be thought of as a circadian rhythm disorder because of disturbance of the circadian control of eating in relation to timing of sleep [195]. Some researchers, however, have suggested that SRED shares a common pathophysiology with arousal disorders because overall sleep disorders are more common in patients with SRED [199]. Because of an association between the restless legs syndrome (RLS) and SRED, a common abnormality in dopaminergic metabolism has also been implicated in its pathophysiology [200].

### **Clinical Symptomatology**

Patients who suffer from SRED often eat high calorie foods that include elaborate preparation which, nevertheless, are careless and lead to unintentional self-inflicted cuts and burns. The episodes tend to arise out of light NREM sleep but may also arise out of REM. They tend to consume unusual items like salt sandwiches, cat

food, and rarely inedible items like soap. Accidental poisoning can occur in addition to weight gain due to SRED. Subjects deny any feelings of hunger and the eating is compulsive. Episodes that last for about 4 min may occur 1–8 times a night [201]. About 90% of patients have complete or near complete amnesia for the event and a minority have vague dream-like mentations [194].

The events can start abruptly as in exposure to sedatives, in the setting psychosocial stressors, or with other sleep disorders or more insidiously without a clear precipitant [198, 202]. The course is progressive and the mean age of onset is 25 with 83% of cases being women [203].

## Epidemiology

Very little epidemiological data is available in the literature but the few papers out there report a prevalence of 1.6% among women [204] another reported the prevalence of SRED to be 6% among insomniacs referred to a sleep center [205] and 10% among obese patients [206]. There is also an odds ratio of 4.9 for the risk of developing SRED among first-degree relatives [207].

## Diagnostic Workup

A careful history and physical exam is important to rule out other sleep disorders and medication exposure that may precipitate episodes of sleep related eating. Sometimes a PSG preferably with an extended EEG montage is required. There are no specific PSG abnormalities seen in SRED but consistently SRED patients have decreased sleep efficiency by about 66–80% [201] and often there are arousals associated with masticatory motor movements [208].

## Treatment

Again, as with the previously discussed parasomnias, SRED can be a comorbid with or secondary to other sleep disorders such as OSAS [209], sleepwalking [194, 210], and RLS [200] so the treatment of the other primary sleep disorder is often effective in controlling SRED as well. Sometimes SRED is iatrogenic, induced by zolpidem [211] or other sedative hypnotic medications such as tricyclic antidepressants, anticholinergics, lithium, triazolam, olanzapine, and risperidone [212], therefore stopping the offending drug usually controls the problem. In primary SRED, melatonin [213] and benzodiazepines appear to be ineffective [212] as do cognitive-behavioral strategies, hypnotherapy and psychotherapy [213]. Low dose pramipexole was reported effective in a randomized, double-blind, placebo-controlled trial [214] and so have SSRIs [215] especially with comorbid depression [203]. The most promising pharmacological intervention is Topiramate, an antiepileptic drug, given at a dose range of 100–400 mg at night, not only reduces nighttime eating, it also improves sleep, and leads to weight loss [96, 216, 217].

## ***Exploding Head Syndrome***

Exploding Head Syndrome (EHS) is a rare and a poorly documented parasomnia that is characterized by a painless loud noise or flash of light at the onset of sleep. It is thought to be a migranous phenomenon [218] [219].

### **Treatment**

The only information we have come from a few case series. Most recommend only reassurance [219–222], after ruling out intracranial vascular lesions such as dissections and aneurysms, as this is a benign phenomenon and most often not frequent enough to be a bother. If the condition becomes disruptive of the patient's sleep then there are anecdotal evidence of efficacy with the tricyclic antidepressant clomipramine 50 mg at bedtime [223], the calcium channel blockers slow-release nifedipine, 90 mg a day (especially when accompanied by a headache) [224], topiramate [218] and flunarizine 10 mg daily [225].

## ***Catathrenia***

Another recently described and rare parasomnia is catathrenia. It was first reported as REM sleep-related expiratory groaning [226] and was later described in NREM sleep as well although not with the same prevalence as in REM described apparently the same phenomenon as “vocalization during prolonged expiration during REM sleep,” 4 and, in our description of nocturnal groaning, we proposed the term of catathrenia (meaning “groaning”) in four cases in which the groaning sounds, though sometimes present also during NREM [227]. The clinical features are quite stereotyped in all reported cases: a silent deep inspiration followed by a prolonged 2–20 s expiration with groaning. There is associated bradypnea during catathrenia, without evidence of respiratory muscular effort or oxyhemoglobin desaturation [228]. It tends to occur in patients without any evidence of other facial, airway, or lung disease and recent intrathoracic pressure recordings show no activity in the diaphragm or the intercostals and normal endoesophageal pressures. During groaning, there is slowing of the respiratory rate by 66% with disproportionate increase in the length of expiration. Breathing otherwise is normal in sleep [229]. The proposed etiology is abnormality in central respiratory center resulting in vestigial, central respiratory pattern during sleep [229].

### **Treatment**

The only reported treatments for sleep-related groaning have been continuous positive airway pressure (CPAP) [227, 230–232], adenotonsillectomy, and mandibular advancement devices [230] even in patients without comorbid sleep apnea.

This has fuelled the controversy as to whether catathrenia is a variant of sleep-related breathing disorder or a distinct parasomnia. Even CPAP has not been reported to be universally helpful and most patients without sleep-related breathing disorder are not likely to use it just for the groaning. The exact mechanism of action of these modalities in catathrenia is unknown but is theorized to be an expansion of the upper airway [230]. Pharmacological treatments, such as clonazepam 0.5–2 mg at bedtime, trazodone 50–100 mg at bedtime, paroxetine 20 mg at bedtime, dosulepine 75 mg at bedtime (a tricyclic antidepressant) [233], gabapentin, pramipexole, and carbamazepine, have been anecdotally tried but failed to control this condition [230].

### ***Sleep-Related Hallucinations***

Although usually associated with narcolepsy, occasional, brief, dream-like imagery occurring either after waking (hypnopompic hallucinations) or just before falling sleep (hypnagogic hallucinations) are common in healthy individuals and generally self-limiting and benign [234]. These are more likely REM sleep phenomenon when it intrudes into wakefulness.

A rare variant of this is the parasomnia known as sleep-related hallucinations. It is characterized by prolonged, vivid, complex, and often visual hallucinations that occur within the major sleep period; usually preceded by awakenings [235]. The hallucinations are almost always visual, colorful and vivid, and often distorted. Initially there is little to no insight into their unreality, the images often disappear when the light is turned on. They only happen after awakening within the major sleep period and never during the day or the major period of wakefulness. In the published case series, there was a large female preponderance of about 92%. Although various etiological factors maybe at play such as exposure to beta blockers, anxiety, dementia, or macular degeneration, the postulated mechanism behind their development is the thalamic block of sensory input which may predispose to hallucination development [235].

### **Treatment**

There is very little information on treatment modalities. Sleep deprivation [234, 236, 237], smoking [234], and certain medications, such as beta adrenergic antagonists [235], sedative hypnotics [234, 237], and certain antidepressants [234], tend to trigger it and often reversing these underlying causes relieve the problem. Among treatments attempted tricyclic antidepressants (nortriptyline and amitriptyline) [235] have been shown ineffective, benzodiazepines have been rarely [238] if at all effective [235] and hypnosis and other psychological interventions have not helped [235]. Because these tend to occur during the night when ambient light is low or absent a parallel has been drawn between it and Charles Bonnet Syndrome



[239, 240], therefore olanzapine at 5 mg a day, a medication shown to be effective in the latter [241], has been tried with alas not data on its efficacy because the few subjects who were started on it were lost to follow up [235].

## Future Directions

More randomized large-scale trials are needed to assess the efficacy of different treatment options used in the management of parasomnias. In addition creating an international registry where information about successful and unsuccessful trials of different therapeutic options can be entered. This will allow us more easily to assess the effectiveness of different therapies in the absence of randomized trials since all the data will be available in one centralized location rather than random case reports that may or may not end up in medical literature databases.

## Conclusion

Parasomnias are common, often benign but sometimes distressing and occasionally dangerous neurological sleep disorders that are poorly studied. They fall into three categories: those arising out of REM sleep, those out of NREM sleep, and a third group that arises out of both states of being. Most information on their treatment comes from case series and open label trials. Effective treatments include both behavioral and pharmacological interventions.

## Summary of Keypoints

- Parasomnias are undesirable physical and experiential events occurring in and around sleep.
- According to the ICSD-2, there are 16 parasomnias divided into three categories.
- The NREM parasomnias or disorders or arousals are three distinct but closely related conditions that include confusional arousals, sleep walking, and sleep terrors.
- The REM parasomnias include sleep paralysis, REM sleep behavior disorder, and the related parasomnia overlap syndrome and nightmares.
- The remaining nine disorders fall under the category of other parasomnias.
- Diagnosis almost always includes polysomnography often with additional EEG or EMG electrodes.
- In overwhelming majority of conditions (nightmares and RBD being the exceptions), treatment is based on anecdotal data and expert opinion.

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# Chapter 18

## Movement Disorders

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**Keywords** Sleep-related movement disorders • Restless legs syndrome • Periodic limb movement disorder • Sleep-related leg cramps • Sleep-related bruxism • Sleep-related rhythmic movement disorder

### Introduction

Sleep-related movement disorders are conditions that are characterized by simple, usually stereotyped, movements or by sleep-related monophasic motor phenomenon, such as leg cramps, that disturb sleep. The Second Edition of the *International Classification of Sleep Disorders* (ICSD-2) includes restless legs syndrome (RLS), periodic limb movement disorder (PLMD), sleep-related leg cramps, sleep-related bruxism and sleep-related rhythmic movement disorder (RMD) under this heading (Table 18.1). RLS is classified within this group of disorders due to its close association with PLMD. Movement alone is not sufficient for the diagnosis of a sleep-related movement disorder as a nocturnal sleep disturbance or a complaint of daytime sleepiness or fatigue is required [1]. Each of these topics will be discussed in this chapter.

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**Table 18.1** Sleep-related movement disorders

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Restless legs syndrome
Periodic limb movement disorder
Sleep-related leg cramps
Sleep-related bruxism
Sleep-related rhythmic movement disorder

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## Restless Legs Syndrome

RLS is a sensorimotor disorder characterized by a distressing urge to move the legs and sometimes other parts of the body such as the arms. The British physician Sir Thomas Willis first described RLS in the seventeenth century by these very descriptive words “Wherefore to some, when being abed they betake themselves to sleep, presently in the arms and legs, leapings and contractions of the tendons, and so great a restlessness and tossings of their members ensue that the diseased are no more able to sleep than if they were in a place of the greatest torture” [2]. The first significant clinical review was carried out by the Swedish neurologist Karl-Axel Ekbom in the 1940s who also coined the term “restless legs” [3]. The severity of RLS can vary from mild with only occasional symptoms to daily severe symptoms that can have a profound effect on sleep and daytime functioning. The pathophysiology of RLS is incompletely understood, but probably results from derangements in iron and dopamine metabolism and has a genetic component [4–6].

## Demographics

The prevalence of RLS varies from region to region, in Europe, South and North America and the Indian subcontinent is estimated to be 4–10% of the adult population, while in Japan, Korea and China, for example, it is 0.6, 0.9 and 1.6% respectively [7–9]. In the United States it is believed to affect more than ten million adults. The 2005 National Sleep Foundation Poll reported RLS symptoms in 8% of men and 11% of Women [10]. Women appear to be at increased risk of RLS as are middle aged or older adults [11]. A population survey study reported that the prevalence of symptoms of RLS was 3% between the ages of 18 and 29 years, 10% between the ages of 30 and 79 years and 19% in persons older than 80 years of age [12].

## Diagnosis

RLS diagnosis is based on clinical grounds and no laboratory study reliably identifies RLS. It does not require a polysomnogram unless an additional sleep disorder is thought to be present. The diagnosis of RLS in adults according to the Second Edition of ICSD-2 requires: (a) The patient reports an urge to move the legs, usually

**Table 18.2** Diagnostic criteria for restless legs syndrome (RLS)

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Uncomfortable sensation in the legs associated with an urge to move
Symptoms are worse at rest
Symptoms are temporarily relieved by movement
Symptoms are worse or only occur at night
The condition is not better explained by another disorder

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accompanied or caused by uncomfortable and unpleasant sensation in the legs. (b) The urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting. (c) The urge to move or the unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues. (d) The urge to move or the unpleasant sensations are worse, or only occur, in the evening or night and (e) The condition is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use or substance use disorder (Table 18.2) [1]. Separate diagnostic criteria have been developed for cognitively impaired adults and young children (age 2–12 years) who have difficulty in reporting these symptoms.

### *Associated Features*

There are several supportive clinical features which, while not required, may assist in diagnosis. These include a response to dopaminergic agents, periodic leg movements (PLMs) and a positive family history for RLS. PLMs may occur in sleep (PLMS) and resting wakefulness (PLMW). PLMS occur in 80–90% of patients with RLS but are not specific for RLS [13]. PLMW may be noted during the wake time on an overnight polysomnogram. A rate greater than 15 PLMW/h of waking supports the diagnosis of RLS. The frequency of RLS among first degree relatives of people with RLS is 3–5 times greater than in people without RLS [14]. There is a negative impact of RLS symptoms on sleep including reports of disrupted sleep, an inability to fall asleep and insufficient hours of sleep [11]. Sleep disruption has also been associated with negative effects on cognitive function in patients with RLS [15]. Onset occurs at all ages from early childhood to late adult life. In children RLS may be misdiagnosed as “growing pains.” Two age-of-onset phenotypes for RLS have been described. Early onset RLS usually starts before the age of 45 years with intermittent symptoms and progresses slowly. Late-onset RLS is usually either stable at onset or rapidly progresses over 5 years to a stable pattern. Patients may describe the symptoms as creeping, crawling, pulling, aching, prickling or tingling. RLS can occur unilaterally or bilaterally in the lower extremities. About half (48.7%) of patients with RLS complain of restlessness in the arms as well. However, every patient who had arm restlessness also had leg restlessness. In most mild cases or RLS, symptoms are localized to the lower extremities and only with increased severity do they also affect the arms and other parts of the body [16]. Peak intensity of RLS symptoms is on the falling phase of the core temperature cycle suggesting that RLS is related to the circadian rhythm [17].

## ***Differential Diagnosis***

The differential diagnosis of RLS includes neuropathic paresthesias, positional discomfort, akathisia, sleep starts (hypnic jerks), PLM disorder, sleep-related leg cramps and pain from other conditions. RLS can be distinguished from positional discomfort as the discomfort is resolved with change of body position without the need for continued movement and an urge to move the legs is not present. Akathisia involves a generalized need to move the body and often in association with neuroleptic medication. Akathisia sufferers frequently report an inner sense of restlessness rather than leg discomfort and lack the circadian pattern characteristic of RLS. Sleep starts produce brief body movements during the transition from wake to sleep and an urge to move is not present. PLMD is a disorder that is only present during sleep without the essential diagnostic features of RLS. Sleep-related leg cramps are painful sensations caused by sudden and intense involuntary contractions of muscles and requires strong stretching to relieve symptoms rather than movement alone. Residual pain is also usually present with sleep-related leg cramps. Pain may be worse at rest but does not include an urge to move the legs. The presence of pain does not exclude a diagnosis of RLS as some patients report their RLS symptoms as pain; however, the additional characteristic features must also be present.

## ***Primary vs. Secondary Factors***

RLS can be classified as primary or secondary. The majority of cases of primary RLS are hereditary (autosomal dominant) with possible loci on chromosomes 12, 14 and 9. Onset of symptoms before the age of 35–45 years indicates an increased risk of RLS occurrence in the family. Physical and neurologic examinations are normal in the majority of primary RLS cases [18]. A number of secondary causes can contribute to RLS and can be expected to improve when the other disorders are treated. Iron deficiency has been associated with RLS. Pathologic studies suggest decreased iron and ferritin in the substantia nigra of RLS patients [19]. Low serum ferritin levels (less than 45 ng/dL) correlate significantly with increased RLS symptoms and with decreased sleep efficiency. A significant correlation to serum iron levels has not been found [20, 21]. Studies suggest disordered transport of iron from the periphery to the central nervous system [22]. The most commonly reported neurologic cause of secondary RLS is peripheral neuropathy [18]. Uremia associated with renal failure has also been identified as a cause of RLS. A 2008 study found that as many as 58.3% of dialysis patients have RLS [23]. Ekblom made the first observation that there is a high prevalence of RLS in pregnancy. In a study of 642 pregnant women 26% were found to be affected by RLS during pregnancy. RLS was strongly associated with the third trimester [24]. A recent study in a French population of women in their third trimester of pregnancy found that 32% were affected by RLS. RLS disappeared after delivery in 64.8% of the women [25]. In a study of 184 narcolepsy with cataplexy patients RLS was found to be significantly

more prevalent compared to controls (14.7% vs. 3%). In this population, RLS symptoms occurred more than 10 years after narcolepsy onset and was less familial and, in contrast to idiopathic RLS, not more prevalent in women [26]. Transient RLS has been described in those undergoing spinal anesthesia [27]. Other secondary causes of RLS include myelopathy, Parkinson's disease and diabetes. Medications may also precipitate RLS symptoms. Common medications which can precipitate RLS include tricyclic antidepressants, SSRIs, MAOIs, lithium, antihistamines and dopamine antagonists. An exception is the antidepressant bupropion with its dopamine promoting activity it may benefit the symptoms of RLS. Though smoking is generally considered an aggravating factor for RLS, there has been one case report describing alleviation of RLS symptoms by cigarette smoking [28]. Caffeine and alcohol also have been described as secondary factors [29, 30].

## ***Management***

Medications that can worsen RLS should be discontinued and secondary causes should undergo evaluation and treatment as this may improve the degree of symptoms. For those found to have iron deficiency iron therapy is recommended. Vitamin C may enhance iron absorption. Non-pharmacologic treatments include improving sleep hygiene as well as daytime exercise, warm baths, leg massage and acupuncture. Two studies, to date, have investigated the effectiveness of sequential compression devices for the treatment of RLS [31, 32]. In a prospective, randomized, double-blinded study, sham-controlled trial there was significant improvement in RLS severity and quality of life measures in those using the sequential compression device compared to the sham devices. Complete relief occurred in one-third of the therapeutic group in this study [32]. There has been one case reporting the improvement in RLS symptoms with 4-week therapy with near-infrared light [33]. A subsequent study, by the same group, with 34 volunteers reported significant improvement in RLS symptoms in the near-infrared light treatment group compared to the control group [34]. More research is necessary to investigate these and other potential non-pharmacologic therapies. RLS has primarily been treated by four classes of medications which include dopaminergic agents, anticonvulsants, benzodiazepines and opioids though other agents have been used (Table 18.3). An evidence-based review produced by a task force commissioned by The Movement Disorder Society concluded that levodopa, ropinirole, pramipexole, cabergoline, pergolide and gabapentin were efficacious for the treatment of RLS while rotigotine, bromocriptine, oxycodone, carbamazepine, valproic acid and clonidine were likely efficacious [35]. Levodopa/benserazide or levodopa/carbidopa at dosages of 100/25 to 200/50 mg is considered efficacious for the treatment of RLS. The side-effect profile of levodopa is favorable however problems with augmentation develop with higher doses and longer treatment duration. The dopamine agonists ropinirole and pramipexole are FDA approved for the treatment of RLS. Ropinirole (0.25–4 mg, mean 2 mg) and pramipexole (0.75 mg) are efficacious for treating RLS in patients with moderate to



**Table 18.3** Treatment for RLS

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Non-pharmacological treatments
Improved sleep hygiene
Exercise
Massage
Acupuncture
Sequential compression devices
Near-infrared light
Pharmacological treatments
Dopaminergic agents
Antiepileptics
Benzodiazepines
Opioids
Iron

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severe symptoms. Several studies have demonstrated the effectiveness of the rotigotine transdermal patch for treatment of RLS including a randomized, double-blinded, placebo-controlled trial including 505 participants with moderate to severe RLS [36–41]. Ergot derived dopamine agonists, including bromocriptine, pergolide and cabergoline require special monitoring due to increased incidence of cardiac valvular fibrosis and other fibrotic side effects. While efficacious these agents are not currently used commonly. Augmentation is the main complication of long-term dopaminergic treatment of RLS and is characterized by an overall increase in severity of RLS symptoms with earlier onset of symptoms, faster onset of symptoms and extension of the symptoms to the upper extremities. Mild cases may be followed while in more severe cases a change in treatment may be indicated. Ferritin may play a role as a biomarker for patients likely to develop augmentation [42]. Side effects of dopaminergic agents include excessive daytime sleepiness, nausea, vomiting, hallucinations and insomnia. Dopaminergic therapy for RLS has also been associated with compulsive behaviors such as compulsive gambling and shopping. Antiepileptics used in the treatment of RLS include carbamazepine, gabapentin, pregabalin and lamotrigine. Antiepileptics may be considered first line therapy in those with concomitant neuropathy or painful leg symptoms. Gabapentin has been reported to be as effective as ropinirole in improving the sensorimotor symptoms in idiopathic RLS [43]. Pregabalin also has been demonstrated to improve RLS symptoms in double-blinded, placebo-controlled trials [44, 45]. Of the benzodiazepines clonazepam is the best documented for treatment of RLS. Side effect of these agents includes sleepiness and tolerance. Opioids are used in the treatment of RLS however at sufficient analgesic doses do cause a series of minor and major adverse effects including sedation, fatigue and constipation. Short acting agents including hydrocodone, oxycodone, and codeine may be used for intermittent or nightly symptoms. For more severe symptoms longer acting opioids including oxycodone, methadone or the fentanyl patch should be used. Tramadol has also been used.

**Periodic Limb Movement Disorder**

Initially termed “nocturnal myoclonus” by the English neurologist Charles P Symonds in 1953, the term periodic movements in sleep was suggested by Coleman in 1980 [46, 47]. PLMD is characterized by periodic episodes of repetitive, highly stereotyped, limb movements that occur during sleep (PLMS) and by clinical sleep disturbance that cannot be accounted for by another primary sleep disorder. PLMS typically involves the extension of the big toe, often in combination with partial flexion of the ankle, the knee, and sometimes the hip. Similar movements can occur in the upper limb. They can occur individually in association with arousals or awakenings from sleep. PLMS may occur unilaterally, alternate between legs or occur simultaneously in both legs. Significant night to night variability may be present.

*Demographics*

In a study of randomly selected community-dwelling persons 65 years and older, the prevalence rate of PLMS was 45% [48]. Although most individuals with RLS have PLMs, most people with PLMS do not have symptoms of RLS.

*Diagnosis*

The diagnosis of PLMD in adults according to the Second Edition of the ICSD-2 requires: (a) Polysomnography demonstrates repetitive, highly stereotyped, limb movements that are: 0.5–5 s in duration, of amplitude greater than or equal to 25% of toe dorsiflexion during calibration, in a sequence of four or more movements and separated by an interval of more than 5 s and less than 90 s. (b) The PLMS index exceeds 5/h in children and 15/h in most adult cases. (c) There is clinical sleep disturbance or a complaint of daytime fatigue and (d) The PLMs are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder (Table 18.4) [1].

<b>Table 18.4</b>	<b>Diagnostic criteria for periodic limb movement disorder (PLMD)</b>
Polysomnography demonstrates repetitive, highly stereotyped, limb movements	
The periodic limb movement index exceeds 15/h in most adult cases	
Clinical sleep disturbance or daytime fatigue	
Limb movements during sleep are not better explained by another disorder	

## ***Associated Features***

Patients often report history of sleep onset or maintenance problems, unrefreshing sleep or excessive daytime hypersomnolence. PLMs have been associated with a number of sleep disorders including narcolepsy, REM sleep behavioral disorder and sleep apnea as well as with a number of neurologic disorders. Bed partner observations of leg movements may help in the clinical evaluation of PLMS. Polysomnography is necessary to identify PLMS and to exclude sleep-related breathing disorders as the cause of the PLMS. PLMS should also be distinguished from other movements such as change in body position, stretching or leg cramps. Movements are reported as an index of the number of leg movements per hour of sleep called the PLMS Index. PLMS may produce no change in the EEG or associated arousal or may be associated with K-complexes, K-alpha complexes, alpha activity or other evidence of arousal. In a study of 23 patients with PLMs and/or RLS 60% of PLMS were associated with microarousals, 4% were associated with slow wave activity and 36% showed no EEG changes. There was a prevalence of leg movements with microarousals in stage N1 and N2 sleep while PLMS without microarousals were prevalent in slow wave sleep [49]. PLMS are usually absent during REM sleep. Two types of PLMS have been described. Type I has a peak frequency between midnight to 3 a.m. followed by a decrease in late morning hours and is seen in those with RLS and idiopathic PLMS. In Type II, leg movements are more evenly distributed throughout the night and are associated with sleep-related breathing disorders, REM sleep behavior disorder and narcolepsy.

## ***Differential Diagnosis***

The differential diagnosis includes sleep starts, normal phasic REM activity and fragmentary myoclonus. Sleep starts are limited to the transition from wakefulness to sleep and are shorter than PLMS. Normal phasic REM activity is usually associated with bursts of rapid eye movements and does not have the periodicity of PLMS. Fragmentary myoclonus activity is briefer and is primarily an EMG diagnosis with little or no visible movement.

## ***Management***

Similar to management of RLS, an investigation to identify secondary causes of PLMs is recommended. Consideration should be given to discontinuing medications that may contribute to PLMs. The decision to treat PLMS should be based on signs of EEG arousal, disturbed nocturnal sleep or associated daytime fatigue. Medication treatment is similar to that of RLS and includes dopaminergic agents, anticonvulsants,

benzodiazepines and opioids. Given that many patients may not be aware of PLMS, assessment of response to therapy is dependent on improvement in sleep quality, bed partner reports on frequency of leg movements and improvement in daytime symptoms including fatigue. In some instances polysomnography performed on treatment is required to assess response to therapy.

**Sleep-Related Leg Cramps**

Sleep-related leg cramps are painful sensations caused by sudden and intense involuntary contractions of muscles or muscle groups, usually in the calf or small muscles of the foot occurring during the sleep period. These episodes may last up to a few minutes, awakens the patient and interrupts sleep.

***Diagnosis***

The diagnosis of sleep-related leg cramps according to the Second Edition of the ICSD-2 requires: (a) A painful sensation in the leg or foot is associated with sudden muscle hardness or tightness indicating a strong muscle contraction. (b) The painful muscle contraction in he legs or feet occurs during the sleep period, although they may arise from either wakefulness or sleep. (c) The pain is relieved by forceful stretching of the affected muscles, releasing the contraction and (d) The sleep-related leg cramps are not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder (Table 18.5) [1].

***Demographics***

Sleep-related leg cramps appear to occur at any age but are more common and frequent in the elderly. In an epidemiologic study in children an overall incidence of 7.3% was reported [50]. In a general practice-based study of 233 people older than age 60, almost one-third had cramps during the previous 2 months, this increased to one-half in those older than 80. In addition, 40% had cramps more than 3 times a week and 6% reported daily cramps [51]. A study of outpatient veterans found that

<b>Table 18.5</b> Diagnostic criteria for sleep-related leg cramps
Painful sensation in leg or foot associated with strong muscle contraction
Painful muscle contraction occurs during the sleep period
Pain is relieved by forceful stretching of the affected muscles
Symptoms are not better explained by another disorder

56% reported leg cramps [52]. Another study found that 50% of patients had leg cramps and 20% reported leg cramps for over 10 years [53]. Sleep-related leg cramps may appear or worsen during pregnancy and was reported in 75% women in their third trimester of pregnancy in a study of 12 women [54].

### ***Differential Diagnosis***

The differential diagnosis of sleep-related leg cramps includes muscle strain, dystonias, claudication, RLS, periodic limb movements and nocturnal myoclonus. The pain associated with muscle strain is often associated with overuse or injury and does not usually occur only at night. The pain associated with claudication is usually relieved by rest. RLS involves an urge to move the legs with temporary relief with movement and not requiring stretching of the muscle. Periodic limb movements occur during sleep and are not associated with pain or muscle hardening. Muscle cramps may also be a feature of a number of other neurologic conditions however these cramps are not usually restricted to nighttime or the legs alone.

### ***Associated Features***

During the cramp the muscles are firm and tender. Tenderness and discomfort in the muscle may persist for several hours after the cramping. Delayed sleep onset and awakenings from sleep are often present with persistent discomfort delaying return to sleep. Patients may need to get out of bed to stand and stretch to alleviate symptoms. Sleep-related leg cramps are not sleep stage specific as they may occur in any sleep stage. Although sleep-related leg cramps are idiopathic in most individuals, a large number of potential contributing factors have been reported. Medications that have been reported to cause leg cramps include diuretics, nifedipine, statins B-agonists, steroids, morphine, cimetidine, penicillamine, and lithium. Medical conditions associated with sleep-related leg cramps include uremia, diabetes, thyroid disease, hypoparathyroidism, hypomagnesemia, hypocalcemia, hyponatremia and hypokalemia. Additional predisposing factors include vigorous exercise during the day, oral contraceptive use, peripheral vascular disease and dehydration. Polysomnography is not routinely recommended for the evaluation of sleep-related leg cramps but may show bursts of increased electromyographic activity over the affected area.

### ***Treatment***

A careful history to identify and treat any precipitating factors is important in patients with sleep-related leg cramps. Patients should be reassured regarding the benign nature of the disease. Adjustment of possible contributing medications

should be considered. Cramps, once present, can be aborted by forcible dorsiflexion of the foot with the knee extended. This is often discovered by patients while dealing with cramps acutely at night and may be all that is required when sleep-related leg cramps are infrequent. Passive massage or stretching may also help. An uncontrolled study of 44 patients determined that passively stretching the calf muscles 3 times a day for several days prevented cramps though a more recent randomized controlled trial found this treatment to be ineffective [55, 56]. Pharmacological treatment of leg cramps may be necessary when symptoms are severe and frequent. A number of treatments have been investigated. Quinine, an alkaloid agent, reduces the excitability of the motor end plate to nerve stimulation and increased the refractory period of skeletal muscle contraction. It has been used to treat leg cramps since 1940 though there are significant concerns regarding the risk/benefit ratio with this drug [57, 58]. Meta-analysis data regarding the efficacy of quinine have produced conflicting data with one study reporting an 8.8% reduction in leg cramps and another reported a 3.6% reduction [59, 60]. In a study of 27 male veterans, 13 reported at least a 50% decrease in the number of leg cramps with quinine treatment [61]. In 1995 the FDA concluded that the risks of quinine outweighed any possible benefit and ordered a stop to the marketing of quinine for prevention or treatment of sleep-related leg cramps. They identified a 1 in 1,000 to 1 in 3,500 risk of potentially fatal thrombocytopenia. If used, risks vs. benefits should be evaluated closely, patients should be aware of the potential risks associated with quinine use and quinine should be used cautiously at the lowest dose possible. Use of quinine containing beverages including tonic water and bitter lemon should be discouraged due to anecdotal reports suggesting that products containing quinine may produce neurological complications [62]. Quinine induced thrombocytopenia and hypersensitivity reactions are among the most serious complication of quinine. Other rare complications include pancytopenia, hemolytic uremic syndrome and hepatitis. Quinine toxicity is also a significant concern. Naftidrofuryl oxalate, a vasodilator, significantly reduced the frequency of cramps and increased the number of cramp free days by a third in a double-blind, placebo-controlled trial in 14 patients [63]. Orphenadrine citrate, an anticholinergic, reduced the frequency of leg cramps by a third in the majority of patients in a double-blind crossover trial [64]. Verapamil 120 mg at bedtime for 8 weeks resulted in an improvement in cramp symptoms in seven out of eight patients during an uncontrolled study [65]. Magnesium was effective in treating sleep-related leg cramps in pregnant women in a double-blind, randomized, placebo-controlled study; however, no significant effect was seen in the study of non-pregnant patients [66, 67]. Vitamin E did not reduce the frequency of leg cramps in a randomized controlled crossover study [61]. In the only randomized, double-blind, placebo-controlled study evaluating the efficacy of vitamin B complex capsules, 86% of the patients had prominent remission of leg cramps at 3 months compared to placebo [68]. Several studies have demonstrated the effectiveness of gabapentin in the treatment of leg cramps in those with neurologic conditions though its usefulness in idiopathic leg cramps remains unclear [69, 70]. The effectiveness of lidocaine injection at the gastrocnemius trigger point and botulinum injection into calf muscles for treatment of sleep-related leg cramps has also been reported [71, 72].

## Sleep-Related Bruxism

One of the first reports of bruxism was from Black in 1886; however, the term bruxism was introduced by Miller in 1938 [73, 74]. Sleep-related bruxism is an oral activity characterized by grinding or clenching of the teeth during sleep usually associated with sleep arousals. Jaw activity during sleep includes tonic contractions and rhythmic masticatory muscle activity (RMMA) that occurs at about 1 Hz. Tooth-grinding sounds occur when these contractions are strong during sleep and are present in about 20% of episodes [75].

### *Demographics*

Bruxism has the highest prevalence in childhood decreases with increasing age. One study reported an overall prevalence of 8% with a frequency of 13% in those 18–29 years of age and only 3% in older individuals [76]. No gender differences have been found [77]. A familial pattern is seen in approximately 20–35% of patients [78]. Moderate to severe tooth wear and jaw discomfort is seen in about 5–10% of the population [75].

### *Diagnosis*

The diagnosis of sleep-related bruxism according to the Second Edition of the ICSD-2 requires: (a) The patient reports or is aware of tooth-grinding sounds or tooth clenching during sleep. (b) One or more of the following is present: abnormal wear of the teeth, jaw muscle discomfort, fatigue or pain and jaw lock upon awakenings, masseter muscle hypertrophy upon voluntary forceful clenching and (c) The jaw muscle activity is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder (Table 18.6) [1]. In routine polysomnography bruxism is suggested by a typical EMG artifact recorded on electroencephalographic recordings. The EMG of bruxism shows either a phasic pattern of activity at 1 Hz frequency lasting 0.25–2 s, sustained tonic activity lasting longer than 2 s, or a mixed pattern.

### *Differential Diagnosis*

Nocturnal jaw movements can be associated with other disorders including partial complex or generalized seizures, idiopathic myoclonus and parasomnias such as sleepwalking and must be distinguished from sleep-related bruxism.

**Table 18.6** Diagnostic criteria for sleep-related bruxism

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Tooth-grinding sounds or tooth clenching during sleep
One or more of the following are present: abnormal wear of the teeth, jaw muscle discomfort, fatigue or pain and jaw lock upon awakening and/or masseter muscle hypertrophy upon voluntary forceful clenching
Jaw muscle activity is not better explained by another disorder

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### ***Associated Features***

Sleep-related bruxism can lead to abnormal wear of the teeth, tooth pain, jaw muscle pain or temporal headache. Fractured teeth and buccal lacerations and temporomandibular joint pain can also occur as a consequence of sleep-related bruxism. Sleep disruption may also occur. Over time, hypertrophy of the facial muscles can develop. Sleep bruxism has been attributed to several etiologies though the theory that malocclusion was the cause has fallen out of favor. It is thought that a combination of psychological stress and specific personality traits may play a role. Other associated conditions include obstructive sleep apnea, gastroesophageal reflux, certain medications including serotonin reuptake inhibitors and amphetamines. Bruxism is frequently associated with Down's syndrome, autism and attention deficit hyperactivity disorder (ADHD) [79, 80]. Bruxism can occur during any sleep stage, including REM sleep, but is most often seen during arousals from stage N2 sleep.

### ***Management***

Therapies for sleep-related bruxism can be divided into orthopedic, behavioral and pharmacologic. Non-pharmacological treatments include occlusal bite splints which provide protection against tooth damage. Patients should be followed by a dentist who can monitor dental wear. Excessively worn teeth may need to be crowned. Obstructive sleep apnea is a risk factor for sleep-related bruxism and successful treatment of sleep disordered breathing may eliminate bruxism during sleep [81]. Psychological counseling may be helpful in stress-related cases of bruxism. Benzodiazepines and muscle relaxants may be necessary in more severe cases though they may contribute to daytime sleepiness. Randomized, controlled and double-blind studies investigating the pharmacologic therapies for sleep-related bruxism are lacking. Other medications that have been reported to be used for bruxism include propranolol, L-dopa, pergolide, bromocriptine, and gabapentin [82–85]. Botulinum toxin injection in the masseter muscles resulted in significant clinical improvement in a group of 18 individuals with severe, recalcitrant, bruxism. The authors suggested botulinum toxin therapy in those who had not responded to conventional therapy [86].



## Sleep-Related Rhythmic Movement Disorder

Described in 1905 by Zappert as “jactatio capitis nocturna” and independently by Cruchet as “rhythmie du sommeil” the term “rhythmic movement disorder” was adopted by the ICSD in 1990. Sleep-related RMD is characterized by repetitive, stereotyped, and rhythmic motor behaviors that occur predominantly during drowsiness or sleep and involve large muscle groups. Initially classified as a sleep wake transition disorder, the revised ICSD reclassifies RMD under the heading of sleep-related movement disorders. Sleep-related rhythmic movements are normal in children and a disorder should be diagnosed when significant consequences are present. RMD is typically seen in infants and children. Body rocking, head banging and head rolling are subtypes of RMD. Combined types may also be observed.

### *Demographics*

SRMD is most commonly observed in children. The incidence of RMD is 66% in 9-month-old infants and decreases to 8% in 4-year olds [87]. In one study, head banging persisted beyond the age of 4 in 30% of patients but usually ended by age 10 [88]. Though most common in children RMD has also reported in adolescents and adults. When observed in older children and adults there has been a reported association with mental retardation, autism or other pathology though cases in adults of normal intelligence have been reported [89, 90]. No sex differences have been found in patients with RMD.

### *Diagnosis*

RMD can be recognized by its characteristic clinical features. However, in some instances polysomnography may be useful. The diagnosis of RMD according to the Second Edition of the ICSD-2 requires: (a) The patient exhibits repetitive, stereotyped and rhythmic motor behaviors. (b) The movements involve large muscle groups. (c) The movements are predominantly sleep related, occurring near nap or bedtime, or when the individual appears drowsy or asleep. (d) The behaviors result in a significant complaint as manifest by at least one of the following: interference with normal sleep, significant impairment in daytime function, self-inflicted bodily injury that requires medical treatment and (e) The rhythmic movements are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder (Table 18.7) [1].

**Table 18.7** Diagnostic criteria for sleep-related rhythmic movement disorder (RMD)

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Repetitive, stereotyped and rhythmic motor behaviors
Movements involve large muscle groups
Movements are predominantly sleep related or occur near nap or bedtime
A significant complaint such as interference with sleep, significant impairment in daytime function or self-inflicted bodily injury is present
Rhythmic movements are not better explained by another disorder

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### ***Associated Features***

While polysomnographic studies have shown rhythmic movements to occur most often in stage N1 and N2 sleep there have been reports of RMD in REM and slow wave sleep [90, 91]. In the case of RMD occurring in REM sleep, concurrent REM sleep behavior disorder has not been reported [90, 92]. The most common subtypes of RMD are body rocking (19.1%), head banging (5.1%), and head rolling (6.3%). Body rolling, head rolling and leg banging subtypes have also been described. As noted previously patients may also have combinations of the noted subtypes. Sleep is not fragmented by RMD and sleep stages do not usually change as a result of movement. RMD does not usually interrupt sleep and patients have minimal recall. A review of ten subjects with RMD persisting beyond 5 years of age found a strong association with ADHD [90]. Several studies have reported RMD in adults with obstructive sleep apnea with RMD initiated by arousals at the termination of the apneas. Improvement in RMD was noted with treatment of obstructive sleep apnea with CPAP [93–95]. Polysomnogram is useful to uncover RMD aggravated by another sleep disorder. On polysomnogram the frequency of movements ranges from 0.5 to 2 Hz.

### ***Differential Diagnosis***

The clinical history of RMD is usually clear though the differential diagnosis of RMD includes PLMD and sleep-related epilepsy. In contrast to PLMD, the movements of RMD are continuous for short periods of time rather than periodic jerking. Polysomnographic findings of RMD may be confused with bruxism, thumb sucking and rhythmic sucking of a pacifier. RMD should also be distinguished from akathisia which is not sleep related and involves a feeling of generalized restlessness.

## ***Treatment***

For the majority of RMD patients no treatment other than reassurance is required. Parents should be advised that neurologic damage is unlikely and that the child will outgrow the problem. RMD has rarely been associated with head injury, carotid artery dissection and ocular injury [96–98]. In cases where there is concern regarding serious injury, treatment is warranted. Hypnosis was reported as an effective treatment in a 26-year-old woman with body rocking since infancy [99]. Other treatments that have been used include behavioral interventions [100]. Almost complete resolution of rhythmic movements was noted in six children with 3 weeks of controlled sleep restriction with hypnotic administration in the first week [101]. Tricyclic antidepressants have also been used to treat RMD. One study documented failure of doxepin, amitriptyline and imipramine while another reported success with imipramine [102, 103]. In one report citalopram at a dose of 20 mg was effective in eliminating head banging in a 5-year old with ADHD [104]. Several studies have demonstrated the utility of low dose clonazepam. Clonazepam at a starting dose of 0.5 mg was not sufficient to decrease the intensity or frequency of events but 1 mg was found to be effective [105, 106].

## **Conclusion**

Sleep-related movement disorders include a varied group of diseases which are quite prevalent and can cause significant sleep disturbance, impairment in daytime functioning and compromise quality of life. These disorders are frequently encountered yet may be confused or misdiagnosed by health care professionals. Increasing awareness of these conditions is necessary to allow for prompt identification and management as this can significantly improve quality of life.

## **Summary of Keypoints**

- Restless Legs Syndrome (RLS) is a common sensorimotor disorder characterized by a distressing urge to move the legs and sometimes other parts of the body such as the arms. RLS affects approximately 10% of US adults. Difficulty falling asleep may frequently be associated with moderate-to-severe RLS.
- The diagnosis of RLS is based on clinical criteria and does not require a polysomnogram unless an additional sleep disorder is suspected.
- The majority of cases of primary RLS are hereditary (autosomal dominant). Causes of secondary RLS include iron deficiency, peripheral neuropathy, uremia associated with renal failure and pregnancy. Common medications which can precipitate RLS include tricyclic antidepressants, SSRIs, MAOIs, lithium, antihistamines and dopamine antagonists. RLS affects approximately 10% of US adults.

- RLS Diagnostic Criteria

1. Uncomfortable sensation in the legs associated with an urge to move
2. Symptoms are worse at rest
3. Symptoms are temporarily relieved by movement
4. Symptoms are worse or only occur at night

- Medications that can worsen RLS should be discontinued and secondary causes should be evaluated and treated.
- Management strategy consists of discontinuation of medications that can worsen RLS, treatment of secondary causes of RLS such as iron deficiency, conservative treatment and pharmacologic treatment. Four classes of medications have been used for the treatment of RLS, including dopaminergic agents, anticonvulsants, benzodiazepines and opioids.
- Periodic limb movement disorder (PLMD) is a sleep disorder characterized by rhythmic movements of the limbs during sleep, involving the legs, but upper extremity movements may also occur. Movements tend to cluster in episodes that last anywhere from a few minutes to several hours.
- The causes of PLMD are unknown. However, people with a variety of medical problems, including Parkinson's disease and narcolepsy, may have frequent periodic limb movements in sleep. PLMD may be caused by medications, most notably, antidepressants. Periodic Leg Movements (PLMs) occur in at least 85% of people with RLS. PLMs are not usually seen in REM sleep.

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# Chapter 19

## Perioperative Care of Patients with Obstructive Sleep Apnea Syndrome

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**Keywords** Perioperative complications • Postoperative monitoring • Obstructive sleep apnea • Questionnaires • Perioperative guidelines • Sleep apnea guidelines • Postoperative CPAP • Hospital sleep apnea

### Introduction

Patients with obstructive sleep apnea (OSA) have an intrinsic defect where disfavorable anatomic features, combined with increased airway resistance, leads to airway compromise when there is an insufficiently countered net upper airway (UA) dilator muscle force [1]. Patients with OSA are therefore more vulnerable during anesthesia and sedation, as the effects of loss of wakefulness and supination are compounded by drug-induced depression of all muscle activity and of arousal responses, so that they cannot respond well to hypoxemia, hypoventilation, or even asphyxia [2, 3]. Conversely, those with difficult airways during anesthesia, either because of problems with maintenance of airway patency without tracheal intubation or because anatomic compromise makes intubation itself problematic, are at increased risk of OSA. As such, difficulty with airway maintenance during anesthesia should prompt further investigation for the possibility of OSA [4, 5]. These relationships are clinically relevant. Early identification of patients with OSA may forewarn the clinician of potential difficulty with airway maintenance intra- and postoperatively, perhaps influencing choice of anesthetic technique and postoperative monitoring environment. Anticipation of perioperative issues in those with known OSA as well as screening

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for those with suspected sleep apnea is now urged by the American Academy of Sleep Medicine (AASM) and the American Society of Anesthesiologists (ASA) [6, 7]. As will be discussed in much more detail below, perioperative complications occur more commonly in those with OSA and can have significant impact on patient outcomes [8]. We will first review the factors that may contribute to increased risk of complications in surgical patients as it pertains to those with OSA. Subsequently, we will discuss preoperative approaches to those with and without known OSA, followed by intra- and postoperative management strategies to optimize care of patients with OSA.

## **Preoperative Risk Assessment and OSA Screening Protocols**

### ***Factors Contributing to Increased Risk of Complications in Surgical Patients***

As introduced earlier, the mechanism of OSA has been related to increased UA collapsibility, reduction in UA size, alterations in craniofacial structure, and enlargement of the surrounding soft tissue [9–11]. During wakefulness, the UA muscles maintain patency despite negative intraluminal inspiratory pressures. During sleep, the UA muscles behave like a collapsible tube that has been likened to a Starling resistor [12]. The airway will collapse if intrathoracic and intraluminal pressure decreases beyond the critical opening pressure, or Pcrit. Normal subjects, primary snorers, patients with obstructive sleep hypopnea, and patients with OSA are distinguished by progressively higher and more positive Pcrit values, signifying progressively higher likelihood of UA collapse [13, 14].

Increased UA collapsibility can contribute to the increased perioperative risk in patients with OSA and can be directly influenced by choice of perioperative medications. Sedatives, anesthetics, and narcotics reduce UA dilator tone and inhibit protective airway reflexes, central ventilatory drive, and mechanisms of arousal [15]. These effects mimic sleep, which can lead to exacerbation of the apneas and hypopneas and this population is already predisposed to this. Also, previously obstructive sleep-disordered breathing events may now become central or complex under the influence of opiates [16]. Intubation and postoperative edema, nasal packing, nasal tubes, and hematomas can narrow the UA. The result is a reduction in the amount of collapse necessary to cause apneas and hypopneas. The requirement for supine positioning perioperatively is another contributor to worsening of OSA, especially in those whose OSA is known to be supine predominant [17]. While supine positioning may especially be a concern for those going home unobserved the same day of surgery, it still poses a challenge in the hospitalized patient and can amplify the above-mentioned risk factors.

The inpatient setting plays host to additional risks for OSA patients. It is well known that hospitalized patients can suffer from sleep deprivation in the

form of sleep fragmentation, circadian disruption, and sleep restriction [18–21]. Postoperative OSA patients are more vulnerable to medical problems when sleep is denied or further compromised by sleep-disordered breathing [22]. Whereas there is a reduction in REM sleep in most hospitalized patients, near-obliteration of REM can initially occur in postsurgical patients which is significantly related to an opioid effect [23].

Personal observation tells us that patients often discontinue use of positive airway pressure (PAP) perioperatively. Patients at times may have PAP appropriately held by their caregivers in the setting of their illness for various reasons. Forgetting to bring the PAP device, failure of the health care provider to restart postoperative PAP, and failure of the hospital to provide equipment can also contribute.

## ***Morbid Obesity and OSA***

Obesity is one of several predictors for OSA [24]. Aside from the problems with redundant pharyngeal tissue and airway collapse, abdominal obesity has mechanical effects on the UA. Studies have demonstrated that the reduced lung volume associated with obesity contributes to poor UA function in OSA patients [25]. Support for this interaction comes from experimental findings where abdominal compression during sleep in OSA patients worsened UA collapse [26]. Historically, the intubation of the morbidly obese patient with OSA and a suspected difficult airway was most commonly managed with an awake, fiber-optic technique. Recent studies have described a 96% success rate when using an alternative airway device called the intubating laryngeal mask airway (ILMA) in morbidly obese patients [27, 28]. In one study, 100% of the morbidly obese patients were successfully ventilated through the LMA [29]. Whether these promising outcomes persist when using an ILMA in the morbidly obese with OSA is not known. Intervention protocols as they relate to PAP therapy and gastric bypass surgery patients will be discussed later.

## **Preoperative Evaluation**

### ***Preoperative Screening for Suspected OSA***

Surgical patients usually undergo preoperative evaluation a few days or weeks prior to their surgery. In 2006, the ASA published guidelines recommending patients be screened for risk of OSA before their surgery [30]. While a number of questionnaires had been developed to aid in identifying patients at risk for OSA, most of these had been first validated in the outpatient sleep laboratory setting. In the last several years, questionnaires had been developed with validation in the preoperative setting [31].

### **The Berlin Questionnaire**

The Berlin questionnaire allows the patient to self-report five questions on snoring, three on excessive daytime sleepiness, one on sleepiness while driving, and one inquiring history of hypertension [32]. It is one of the commonly known questionnaires for OSA and has been validated in the setting of primary care. Age, gender, weight, height, and neck circumference are also recorded. The Berlin questionnaire's predictive performance is patient populations dependent. In a primary care setting of 744 patients, it carries a sensitivity of 0.89, specificity of 0.71, and half of the high-risk patients it identifies are subsequently found to have OSA (at AHI >15) by polysomnography. The Berlin Questionnaire identified 24% of patients presenting for elective surgery as high risk of a pool of 318 [33]. A study screening preoperative patients using the Berlin questionnaire determined it had a sensitivity of 69% with a specificity of 56% in surgical patients [34]. Even if the Berlin questionnaire has moderately high sensitivity and specificity for identifying OSA in the preoperative setting, the number of questions and the complicated scoring procedure may be too laborious for anesthesiologists and their patients.

### **The American Society of Anesthesiologists' Checklist**

In the recent guidelines for the perioperative management of patients with OSA, the ASA taskforce on OSA developed a 14-item checklist to assist anesthesiologists in identifying OSA [30]. Patients endorsing symptoms or signs in two or more of the three categories (physical characteristics, history of airway obstruction during sleep, and complaints of somnolence) are considered high risk of having OSA. The major drawback to this screening tool is the time commitment because the checklist needs to be completed by the clinician. The ASA check list has been validated in surgical patients to have sensitivities of 72, 79, and 87% at AHI cutoff levels of >5, >15, and >30 events/h, respectively [34]. The same validation study also found the ASA checklist's sensitivity and specificity in predicting OSA in surgical patients similar to the STOP questionnaire discussed below.

### **The STOP Questionnaire**

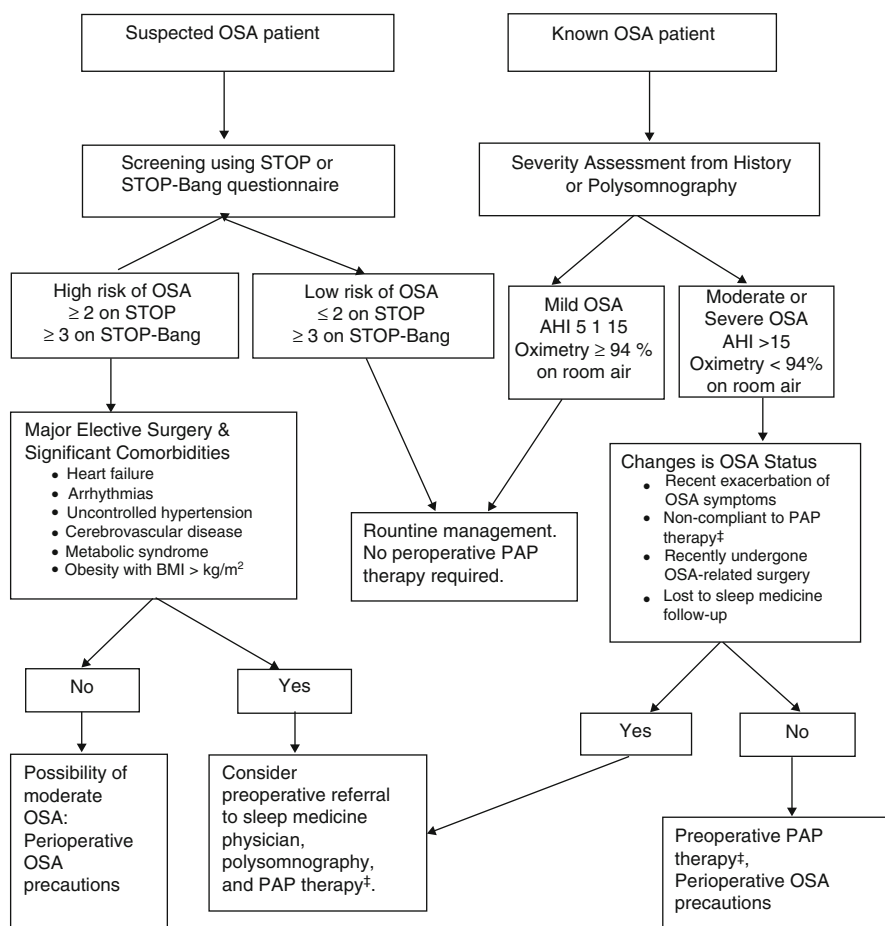
A condensed modification of the questions in the Berlin survey, the STOP questionnaire was developed and validated to facilitate the widespread usage of an OSA screening tool in surgical patients (S: Snore loudly, T: daytime Tiredness, O: Observed to stop breathing during sleep, P: high blood Pressure). The sensitivity of the STOP questionnaire at an AHI of >15 and >30 events/h cutoff levels was 74 and 79%, respectively, with specificity at similar AHI levels of 53 and 49%, respectively [35].

## The STOP-Bang Model

When additional factors were included, the STOP-Bang Questionnaire had the highest sensitivity, especially for patients with moderate to severe OSA. This combined version of the STOP-Bang Questionnaire added demographic and physical features (B: BMI  $>35$  kg/m<sup>2</sup>, A: Age  $>50$  years, N: Neck circumference  $>40$  cm, G: male Gender). The use of the STOP-Bang Questionnaire improved the sensitivity to 93, and 100% at AHI cut-offs of  $>15$  and  $>30$ , respectively, making it highly sensitive and an ideal screening tool. The specificity of the STOP-Bang Questionnaire at similar AHI levels, however, was only 43 and 37%, respectively. In the preoperative clinic, the STOP Questionnaire was used to screen 211 patients, 28% of whom were classified as being at high risk of OSA [35]. Ramachandran and Josephs [36] analyzed the accuracy of clinical screening methods in the diagnosis of OSA in a meta-analysis. The authors identified 26 different clinical prediction tests with 8 in the form of questionnaires and 18 algorithms, regression models, or neural networks. The authors concluded severe OSA can be predicted by questionnaires and clinical tests with a high degree of accuracy. The Berlin questionnaire, the Sleep Disorders Questionnaire, morphometry (Kushida index) [37] and the combined clinical–cephalometry model (Battagel) [38] were the most accurate questionnaires and clinical models. However, they warned that the high degree of heterogeneity and false negative rate with all questionnaires and most clinical prediction models makes it possible that a significant proportion of patients with OSA could still be missed by all questionnaires and most of the clinical models. The metaregression analysis revealed that clinical models, log equations, combined techniques, cephalometry, and morphometry were significant test characteristics, whereas body mass index, history of hypertension, and nocturnal choking are significant test elements in the more accurate prediction models.

## Sleep Apnea Clinical Score

A different simple OSA screening questionnaire, called the Sleep Apnea Clinical Score (SACS) was validated in the outpatient sleep laboratory environment and shown to have a high positive predictive value for OSA [39]. The SACS score was initially validated in postsurgical patients to identify patients who desaturated in the postoperative hospital ward area [40]. A large follow-up prospective study enrolled nearly 700 patients using the SACS and showed that a higher risk of OSA (32% of all patients) was associated with a much higher likelihood of a postoperative 4% oxygen desaturation index (ODI)  $>10$  events/h and recurrent postanesthesia care unit (PACU) respiratory events [41]. Subsequent postoperative hospital ward episodes of respiratory complications were also associated with a high SACS (odds ratio 3.5,  $P<0.001$ ), especially if they also had recurrent respiratory events in the PACU during 90 min of observation, whereby the likelihood of a postoperative respiratory event was markedly increased (odds ratio 21.0,  $P<0.001$ ). There was no significant benefit with the SACS questionnaire in predicting cardiac complications or prolonged hospital stay.



**Fig. 19.1** An approach to those with suspected or known obstructive sleep apnea (OSA) prior to surgery in the ambulatory setting. ‡ Positive airway pressure (PAP) therapy may include continuous, bilevel, or autotitrating PAP (adapted with kind permission from Springer Science + Business Media [42])

The decision regarding which screening tool is most suitable lies with the clinicians and their institutional experience. Optimal preoperative evaluation takes into account the risk of the surgery as well as the risk of the patient having undiagnosed OSA [42]. The left side of Fig. 19.1 summarizes a preoperative approach in the suspected OSA patient. Those with  $\geq 2$  on STOP or  $\geq 3$  on STOP-Bang criteria are considered high risk of having undiagnosed OSA. If a high-risk patient is presenting for major elective surgery and has significant comorbidities suggestive of long-standing severe OSA, the anesthesiologist should consider a preoperative referral to the sleep physician and a recommendation for a polysomnogram

or a multichannel home sleep test if resources permit. A timely and early consult would allow the sleep physician adequate time to prepare a perioperative management plan, which may include a period of home PAP treatment. Major elective surgery may have to be deferred in patients with a high clinical suspicion of severe OSA with systemic complications. Ultimately, the decision for further preoperative sleep study testing will depend on the clinical judgment and expertise of the attending physician, taking into account the patient-specific and logistical considerations in their totality.

On the other hand, there may be patients who are at high risk according to the OSA screening questionnaires, but who otherwise are without significant comorbidities and are ambulatory surgery patients or at least not scheduled to undergo major surgery [43]. Some of these patients may have had uneventful anesthetics in the past. These “at risk” patients may represent false positives on screening or represent patients with less severe OSA (AHI <15). A positive screening test would raise awareness and alert the anesthesiologist to undertake perioperative precautions for possible OSA, as discussed later in the chapter. It can be assumed that these patients possibly have moderate to severe OSA, and if subsequent intraoperative (e.g., difficult airway) [44] or postoperative events (PACU recurrent respiratory events) [41] suggest a higher probability of OSA, a polysomnography, and a sleep physician referral after the surgery may be indicated. Due to the high sensitivity and negative predictive value of the OSA screening tools, the incidence of false negatives should be low. Therefore, patients who are at low risk of OSA ( $\leq 3$  positive responses on STOP-Bang) are unlikely to have OSA. These patients may expectedly be managed with routine perioperative care.

### ***Preoperative Evaluation of Known OSA***

A preoperative evaluation approach for known OSA patients is illustrated on the right side of Fig. 19.1. To start, the diagnosis and severity of OSA should be confirmed. Long-standing OSA may have systemic complications, including hypoxemia, hypercarbia, polycythemia, and cor pulmonale. Pulse oximetry may be a simple screening tool in the preoperative clinic. Some advocate that an oxygen saturation value of <94% on room air in the absence of other causes should be an alert flag for possible severe long-standing OSA [42]. The possibility of comorbidities, such as uncontrolled hypertension, arrhythmias, cerebrovascular disease, heart failure, metabolic syndrome, and obesity should be pursued. The use of PAP devices (continuous PAP, bi-level PAP, auto-titrating PAP) and the compliance to PAP therapy should be assessed for those who have been prescribed PAP therapy. It may be necessary to refer some patients with known OSA to the sleep medicine physician for preoperative reassessment, especially patients who have been lost to sleep medicine follow-up and are noncompliant with therapy, those who have had recent exacerbation of OSA symptoms, and those who have undergone OSA-related airway surgery.

## ***Preoperative OSA Optimization***

Reinitiation of preoperative PAP in the noncompliant OSA patient should be considered, although evidence of its efficacy is lacking in this preoperative context [45]. Patients with moderate and severe OSA who have been on PAP therapy should continue PAP therapy in the preoperative period [30]. The intraoperative anesthesia team should be alerted in advance, and perioperative OSA precautions should be undertaken. Some of these measures would include anticipating possible difficult airway experiences, the use of short-acting anesthetics agents, opioid minimization, full reversal of neuromuscular blockade verified prior to extubation, and extubation in a nonsupine position. It is unclear from the current literature if mild OSA (AHI 5–15) would be a significantly worse disease entity under anesthesia and in the perioperative period. Based on expert opinion referenced earlier, patients with mild OSA would not require preoperative PAP therapy. Mild OSA patients without respiratory events in the PACU may be managed with routine perioperative care.

## **Intraoperative OSA Management**

### ***Choice of Anesthetics/Anesthetic Technique***

There are numerous reviews on the subject of anesthetic management of OSA patients [46–49] that emphasize that the type of anesthesia may have differential impact on the respiration of patients. Despite these reviews, there are no randomized controlled trials of the safety of various anesthetics in the perioperative period. As mentioned previously, different analgesics have different margins of safety and result in varying levels of respiratory depression. A relatively recent study [50] has documented the impact of propofol on UA collapsibility by investigating the relationship between varying concentrations and the critical airway closing pressure or Pcrit discussed earlier. The use of healthy individuals (not patients with OSA) as subjects coupled with the lack of a randomized controlled design is a significant limitation of this study. Nevertheless, the findings highlight that a carefully chosen concentration of anesthetic may play an important role in the airway management of OSA patients.

An important consideration in the choice of inhaled anesthesia is the presence of any carryover anesthetic effects into the postoperative period that could impair respiration and/or enhance the deleterious respiratory effects of analgesics. In OSA patients undergoing UPPP, there was delayed recovery in those patients receiving isoflurane vs. propofol [51]. Propofol anesthesia was found to result in better oxygen saturation in the first postoperative hour and more rapid recovery of spontaneous breathing vs. isoflurane. Again, these studies were not done on OSA patients. Short-acting anesthetics, such as remifentanyl, have also been shown to result in a rapid postoperative recovery, better oxygen saturation profile, and shorter



postoperative length of stay [52, 53]. Also, morbidly obese patients who underwent major abdominal surgery awoke significantly faster after desflurane than after sevoflurane anesthesia. The patients anesthetized with desflurane had higher oxygen saturation on entry to the PACU [54].

Premedication sedatives, especially benzodiazepines, such as flunitrazepam or midazolam, have been shown to cause postoperative airway obstruction [55]. In this study, 12 patients did not have a premorbid history of OSA but were observed to snore loudly postoperatively. Conversely, some premedication drugs have been shown to be beneficial in OSA patients. In a case report of a morbidly obese woman with tracheal stenosis, dexmedetomidine, an alpha-2 adrenergic agonist, was used as a premedication due to its anxiolytic and sedative properties. The benefit of dexmedetomidine is the lack of significant respiratory depression within the clinical dose range. Similarly, in a randomized controlled trial, orally administered clonidine was found to reduce the propofol dose required for induction of anesthesia [56]. Unfortunately, there are no trials of the efficacy of varying premedication drugs in OSA patients undergoing surgery, but the above studies illustrate their potential importance.

### ***Increased Risk of Difficulty with Tracheal Intubation***

Difficult tracheal intubation and OSA seem to share similar etiological pathways that explain the predisposition to UA abnormalities. A retrospective case-controlled study of 253 patients was conducted to determine the occurrence of difficult intubation in OSA patients [57]. The OSA patients were matched with controls of the same age, gender, and type of surgery. Difficult intubation was assessed by laryngoscopy using the Cormack and Lehane classification [58]. Difficult intubation was found to occur 8 times as often in OSA patients vs. controls (22% vs. 3%,  $P < 0.05$ ). In OSA patients undergoing ear, nose, and throat surgery, a 44% prevalence of difficult intubation has similarly been reported [59]. Furthermore, patients with severe OSA ( $AHI > 40$ ) were found to have a much higher prevalence of difficult intubation [60]. A study of more than 1,500 nonobese and obese patients concluded that increased age, male gender, pharyngo-oral pathology, and the presence of OSA are all associated with a more frequent occurrence of difficult intubation [61]. Conversely, patients with difficult tracheal intubation have been shown to be at greater risk of having OSA [4]. In a small retrospective study of 15 patients with difficult intubation, 53% (8 of 15) of patients were diagnosed with OSA. In a prospective study, 66% of patients with difficult intubation were subsequently found to have  $AHI > 5$  [5]. These reports suggest that anesthesiologists should refer patients with difficult intubation for PSG sleep investigation of OSA. Apart from the above-mentioned studies, there is no research investigating the causal and anatomical relationship between OSA and difficult tracheal intubation and the implications for perioperative management. Despite the higher prevalence of OSA in patients with difficult intubation, it needs to be determined whether it is cost effective for all

patients with difficult intubation to undergo a diagnostic sleep study and if preoperative continuous PAP (CPAP) treatment could ameliorate the difficulty with tracheal intubation.

## **Postoperative OSA Management**

### ***Postoperative Pain Control***

Postoperative analgesia can adversely influence respiration in surgical patients with OSA. In a retrospective study of 1,600 patients, not specifically OSA patients, who had received postoperative patient-controlled analgesia with IV opioids, eight cases of serious respiratory depression were reported [62]. Contributing factors were the concurrent use of a background infusion of opioids, advanced age, concomitant administration of sedative or hypnotic medications, and a preexisting history of sleep apnea. Two retrospective reviews of more than 1,000 surgical patients indicated that postoperative respiratory depression after morphine-based patient-controlled analgesia was observed to occur in about 1–2% of patients [63, 64]. This respiratory depression occurred between 2 and 31 h after initiation of the IV patient-controlled analgesia [63] indicating the need for extended diligent patient monitoring.

A review conducted to identify the risk factors for respiratory depression subsequent to patient-controlled analgesia concluded that there is no single indicator for respiratory depression but that OSA, whether suspected or verified by patient history, is one of the risk factors for respiratory depression [65]. Other factors include older age, hepatic, pulmonary, or cardiac disease, concurrent use of central depressants, obesity, and higher bolus doses of patient-controlled analgesia.

There are no prospective randomized studies examining the respiratory effect of patient-controlled analgesia in OSA patients. In general, the consensus is that opioids are to be avoided in OSA patients, if possible, especially when they undergo UA surgical treatment for OSA [66]. The ASA guidelines recommend regional anesthesia to reduce the possibility of negative adverse events associated with systemic opioids; however, there is little outcome-based evidence to support this [67]. A multimodal approach with combinations of analgesics from different classes and different sites of analgesic administration is a prudent strategy for perioperative pain management [68–70]. Such an approach may include peripheral nerve block catheters or neuro-axial catheters dispensing local anesthetic agents (without opioids) and opioid-sparing analgesic agents, such as nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, acetaminophen, pregabalin, tramadol, and dexamethasone [71].

Other novel approaches, such as ketamine, clonidine, or gabapentin can be used [56, 68–70]. Ketamine may have a stabilizing effect on the UA [72]. In a case report, the nonopioid sedative dexmedetomidine [73] has been shown to reduce the need for postoperative opioids. More recently, it was demonstrated in a double-blinded, placebo-controlled, crossover study that opioid-induced ventilator depression can

be selectively antagonized in humans by co-administering ampakine [74]. Other techniques that avoid medication, such as transcranial magnetic stimulation [75] are also being investigated. A major drawback of these studies is that they are predominantly case reports. Unfortunately, there are no studies comparing the safety and efficacy of different anesthesia technique, general anesthesia, regional anesthesia, or monitored anesthesia care in OSA patients undergoing surgery or studies on different analgesic or adjuvants.

## Postoperative Monitoring

### *Oximetry*

Anesthesiologists regard continuous pulse oximetry monitoring in the perioperative arena as a standard of practice and presumably can prevent postoperative complications and improving patient outcomes. Clinicians naturally assume that corrective measures can be initiated to resolve postoperative hypoxemia to the benefit of patients. Pedersen et al. [76] performed a medical literature search for randomized controlled trials conducted during the perioperative period of patients using mandatory pulse oximetry or not. The authors asked whether pulse oximetry could identify events that led to the prevention of adverse outcomes. The search provided data from nearly 23,000 patients in five reports and as might be expected, the pulse oximetry group showed that oxygen saturation was reduced in the operating room and particularly in the PACU. No statistically significant differences were observed in respiratory, cardiovascular, infectious, or neurologic complications between the two groups. Other important endpoints such as transfer to an ICU, duration of hospital stay, and overall mortality were not reduced with the use of routine oximetry in a general care area in the subset of patients who recently underwent cardiothoracic surgery. Now that pulse oximetry monitoring is so ingrained into the perioperative setting, it is unlikely that we will see randomized outcome-based studies with control groups that include patients with no oximetry monitoring.

The role of home oximetry in the preoperative evaluation of patients considering surgery to predict postoperative complications has been explored. Hwang et al. [77] used home oximetry to screen for potential sleep-disordered breathing in nearly 200 patients prior to elective surgery who had clinical evidence of OSA and used the 4% ODI to see if this was predictive of postoperative complications. A significantly higher rate of postoperative complications were seen in the 57% of the patients with a 4% ODI >5/h (15.3% vs. 2.7%,  $P < 0.01$ ) with an adjusted odds ratio of 7.2. Most of the complications, however, were respiratory and simply required administration of more supplemental oxygen and there were relatively few overall events. Preemptive home oximetry in suspected OSA patients was not useful in predicting hospital stay or other complications nor did it have any impact on major outcome improvement.

## **Capnography**

Since oximetry has not been shown to be a clear outcome benefit in perioperative patients, it was natural to seek other monitoring modalities. End-tidal carbon dioxide tension (ET-CO<sub>2</sub>) and transcutaneous carbon dioxide monitoring (tc-CO<sub>2</sub>) accuracy have been compared in a sleep laboratory with PaCO<sub>2</sub> levels in patients wearing a nasal cannula or using nocturnal positive-pressure ventilatory assistance [78]. ET-CO<sub>2</sub> tension and tc-CO<sub>2</sub> during diagnostic and therapeutic sleep studies did not accurately reflect the simultaneous PaCO<sub>2</sub> levels when PAP therapy was applied. It is not surprising that ET-CO<sub>2</sub> and tc-CO<sub>2</sub> are utilized more for trend observations as opposed to equivalent arterial PaCO<sub>2</sub> levels.

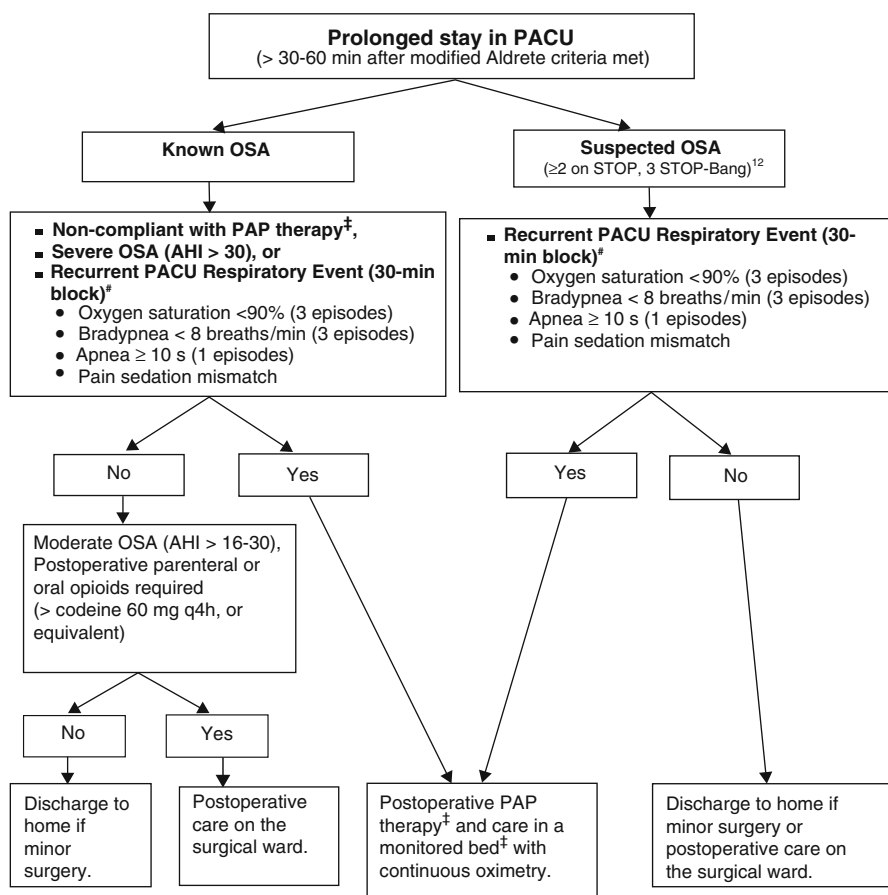
Another investigation was undertaken in patients with and without OSA during recovery from general anesthesia to compare the accuracy of oral guide nasal cannula vs. sidestream capnometry and compared to an arterial PaCO<sub>2</sub> values determined simultaneously [79]. Mainstream capnometry was superior to sidestream capnometry in both obese and nonobese patients. The study did not evaluate outcome benefit or try to predict adverse consequences so the role for capnography as an adjunct monitor to oximetry in postoperative patients remains unclear.

## **Management Algorithms**

### **PACU**

Optimal postoperative monitoring for the OSA patient must take into account the surgery type and risk, patient characteristics, as well as anesthesia and analgesia-specific factors. The 2006 ASA guidelines, directed by expert consensus in the absence of good clinical evidence at the time, urged guidance of OSA patient disposition by a weighted scoring system and patient risk factors [30]. Perioperative risk was broadly divided into severity and treatment of OSA, invasiveness of the surgery and anesthesia used, and postoperative opioid requirements. The scoring system was somewhat involved and did not take into account the importance of recurrent PACU events in predicting more episodes of oxygen desaturation and increased postoperative respiratory complications [41].

Taking into account 2006 ASA guidelines and recent evidence for identifying patients most at risk for postoperative respiratory complications, Seet and Chung [42] proposed an algorithm using recurrent PACU events as a predictive indicator to guide postoperative disposition of the known or suspected OSA patient (Fig. 19.2). A PACU event occurs if in one 30-min time block, the patient has any of the following: (1) apnea for  $\geq 10$  s (only one episode needed for yes), (2) bradypnea of  $\leq 8$  bpm (three episodes needed for yes), (3) desaturations to  $< 90\%$  (three episodes needed for yes), or (4) pain-sedation mismatch, as characterized by high pain scores and high sedation levels observed simultaneously.



**Fig. 19.2** Postoperative management of the known or suspected OSA patient after general anesthesia. Number of occurrence of more than one set of events in each 30-min evaluation period while in the postanesthesia care unit (PACU), including repeat occurrence of the same event set. ‡PAP therapy may include continuous, bilevel, or autotitrating PAP. †Monitored bed – inpatient area that would lend itself to early nursing intervention and includes continuous oximetry monitoring (e.g., intensive care unit, step-down unit, or remote pulse oximetry with telemetry in surgical ward) (adapted with kind permission from Springer Science+Business Media [42])

Recurrent PACU events occur when any one of the PACU respiratory events occurs in two separate 30-min time blocks (not necessary to be the same event or consecutive periods). Patients who are at high risk of OSA on the screening questionnaires and have recurrent PACU respiratory events are more likely to have postoperative respiratory complications. It may be prudent to monitor these patients postoperatively with continuous oximetry in an area where early medical intervention can occur. The monitoring can occur in the step-down unit, on the surgical ward near the nursing station, or with remote pulse oximetry with telemetry (Fig. 19.2).

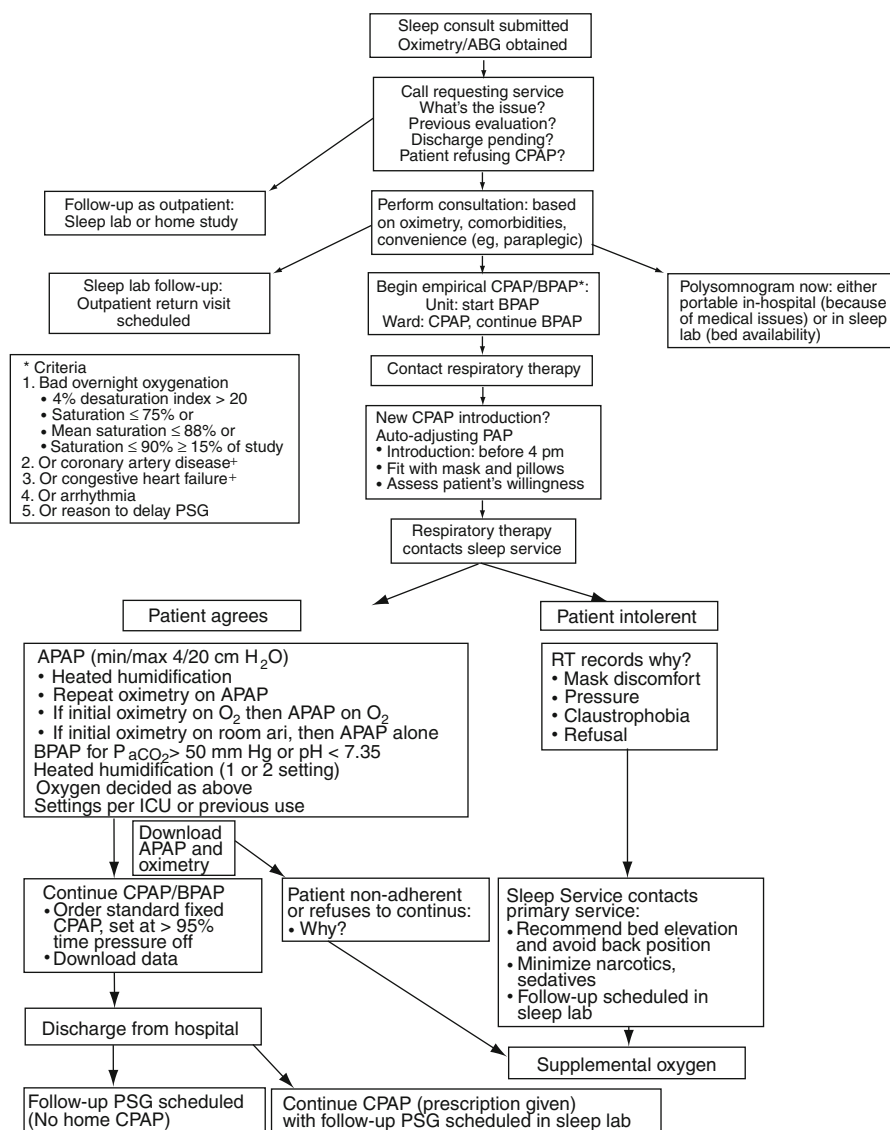
Close postoperative monitoring would certainly be called for in patients with known OSA with recurrent PACU events, but also in their absence if the patient's OSA is severe or if they are noncompliant (left side of Fig. 19.2). In the absence of severe OSA, noncompliance, and recurrent PACU events, patients with moderate OSA or requiring parenteral or higher dose oral opioids (codeine 60 mg every 4 h or equivalent) may be managed postoperatively on the surgical ward with periodic oximetry monitoring. It may also be expedient to place patients requiring postoperative parenteral opioids on supplemental oxygen [80]. The ultimate outcome benefit of the interventions has yet to be demonstrated.

It is not difficult to imagine how the pulmonologist would be called to evaluate either a known, suspect (or even previously unsuspected) OSA patient postoperatively for the aforementioned recurrent PACU events. For those with previously undiagnosed but suspected OSA in the postoperative or medical inpatients setting, our institution has developed an obstructive apnea systematic intervention strategy (OASIS) protocol, as outlined in the top half of Fig. 19.3. PACU or overnight oximetry, ABG, inpatient events, and discussion with the primary team are often enough to guide initial decision making. Appropriate setting (outpatient vs. inpatient) and timing (before or after discharge) of polysomnography can often be difficult and will depend on local resources and lab availability.

Decision for attempted initiation of empiric PAP is also important, as indicated by poor overnight or PACU oxygenation, coronary artery disease, congestive heart failure, arrhythmia, or other reasons. In those for which an attempt at inpatient PAP initiation is warranted, early assessment (prior to 4 p.m.) by the respiratory therapist mask fit and patient willingness is recommended. Once PAP therapy continuation is decided for in the context of the respiratory therapist's assessment, close follow-up is needed to assess patient tolerance. In the case of intolerance, reasons must be assessed. In the case that PAP is tolerated, there is commonly room for fine tuning and optimization until the patient undergoes a full polysomnography. This imperative follow through of inpatient PAP initiation is outlined in the bottom half of Fig. 19.3.

Known OSA patients who have been noncompliant with PAP therapy or have severe OSA may have to be fitted with postoperative PAP therapy and cared for in a monitored environment with continuous oximetry, particularly if there has been recurrent PACU respiratory event. Known OSA patients previously on PAP therapy should be encouraged to be compliant with PAP therapy postoperatively, and PAP therapy should be ordered postoperatively, beginning in the PACU. Preliminary studies have revealed that normalization of sleep architecture and AHI tends to be delayed as far out as the seventh postoperative night [81]. Further outcome-based research on the postoperative management of OSA patients is essential.

Disagreement exists as to whether OSA patients should be discharged for home after surgery. The ASA guidelines highlighted that superficial surgeries or minor orthopedic surgery using local or regional techniques and lithotripsy may be performed on an ambulatory basis [30]. In our opinion, mild OSA patients (AHI 5–15), who have undergone minor surgery without recurrent PACU respiratory events and who do not require high doses of oral opioids for analgesia, may be discharged



ABG = arterial blood gas. CPAP = continuous PAP. BPAP = bi-level PAP. PSG = polysomnography. APAP = auto-adjusting PAP. PSG = polysomnography. RT = respiratory therapy.

**Fig. 19.3** Obstructive apnea systematic intervention strategy (OASIS) for assessing postoperative or medical patients for sleep-disordered breathing, with follow-through management algorithm based on patients' PAP willingness. ABG Arterial blood gas; CPAP continuous PAP; BPAP bi-level PAP; PSG polysomnography; APAP auto-adjusting PAP; PSG polysomnography; RT respiratory therapy (adapted from [22])

home at the discretion of the attending physicians (Fig. 19.2). Ambulatory surgical centers managing OSA patients should have transfer agreements to inpatient facilities and should be equipped to manage contingencies associated with OSA.

## **Intervention Protocols**

### ***General Surgery***

Despite a paucity of data, interest remains high in improving outcomes in those with known or suspected sleep-disordered breathing through preemptive or protocol-directed PAP therapy. By reviewing three cases, Bolden et al. [82] illustrate issues in OSA patients that occurred prior to and after implementation of an OSA protocol. When CPAP was becoming increasingly available in the early 1990s, one hospital mandated a protocol to treat all postoperative patients with CPAP. This came in response to a postoperative death in an OSA patient in which CPAP was withheld, shortly followed by rescue of a postoperative patient from serious complications after treating with CPAP [83]. Of the subsequent 14 patients, in which CPAP was given preoperatively and for 24–48 h postextubation with all subsequent sleep, none developed major respiratory complications. Though the data was limited, the authors advocated for increased awareness of OSA patients and argued for CPAP before and after surgery.

### ***Intervention Protocols in Orthopedic Surgery***

In one prospective study, high-risk OSA patients planning to have orthopedic surgery were identified by using the SACS score. Patients were then randomized to receive routine postoperative care either with or without autotitrating PAP. They aimed to determine the accuracy of the SACS score in predicting whether high-risk OSA patients would have postoperative sleep-related desaturations or a respiratory disturbance index  $>15$ , and the benefit they may gain from anticipatory CPAP therapy [45]. Of 42 patients enrolled, 9 were observed as low risk, while the remaining 33 underwent randomization after being deemed high risk for OSA. The SACS score was found to be 85% sensitive in detecting those with a postoperative respiratory disturbance index  $\geq 15$ . While their lower risk counterparts were not immune to significant oxyhemoglobin desaturation or respiratory events on their first postoperative night, events were less severe than for those in the high-risk group. Interestingly, patients spend less time at or above 90% oxygen saturation on the night prior to discharge (most often postoperative day 4) in comparison to the night immediately following surgery. As discharge approaches, patients are often taken off empiric supplemental oxygen and continuous monitoring, making lending the OSA patient more susceptible to REM rebound postoperative day 3 and beyond.



Preemptive CPAP use did not significantly affect outcomes when used in patients with high clinical suspicion for OSA. The lack of difference was thought due to more than half of the patients' lack of compliance with and intolerance of PAP, often in the setting of substantial postoperative pain.

### ***Intervention Protocols in Gastric Bypass Surgery Patients***

Special consideration of the morbidly obese patient for harboring perioperative risk has been discussed. Aside from sleep-disordered breathing, respiratory risk also extends to atelectasis, abnormal gas exchange, and impaired clearance of secretions. A multicentered observational study prospectively evaluated major adverse outcomes at 30 days in patients undergoing bariatric surgery at ten sites within the United States [84]. Diagnosis of OSA, impaired functional status, and history of deep vein thrombosis or pulmonary embolus were factors independently associated with an increased risk of the composite end point.

Although continuous and bi-level PAP effectively treat these problems, postgastric bypass PAP therapy has not been universally adopted out of concern that positive pressure can cause anastomotic leaks by way of massive bowel wall distention [85]. Opponents of PAP therapy in this setting report no differences in outcomes when comparing known OSA patients who were using preoperative PAP therapy or not, as well as those with no known OSA [86]. The majority of patients in that review (811) were without known OSA, followed by 144 PAP-dependent and 140 non-PAP dependent patients with known OSA. In the absence of any reported anastomotic leaks or deaths, 1, 3, and 6 pulmonary complications were noted in the PAP dependent OSA, non-PAP OSA, and no known OSA groups, respectively.

The majority of practicing pulmonologists would have difficulty withholding postoperative PAP therapy from those who clearly need it on the basis of decreasing risk of possibly overexaggerated pressurized air complications. To assess the safety and efficacy of postoperative PAP after Roux-en-Y gastric bypass, one study prospectively evaluated risk of subsequent anastomotic leaks and pulmonary complications [87]. Of the 1,067 patients included, 420 had known OSA, only 159 of which were using CPAP. While no episodes of pneumonia were diagnosed in any of the patients, only 2 of the 15 major anastomotic leaks occurred in patients treated with CPAP, and there was no correlation found between the two ( $P=0.6$ ). There is some evidence that bi-level PAP therapy improves pulmonary function after open Roux-en-Y gastric bypass, based on a small single-center prospective study [88]. Baseline pulmonary function tests were performed on 27 patients, who were randomized to then receive either conventional postoperative care or bi-level PAP. Preoperative expiratory flow reduction found in both groups was not statistically significant between the groups. In the group receiving bi-level PAP therapy, forced vital capacity, FEV1, and oxygen saturation were significantly higher in comparison to the control group. Despite these findings, bi-level PAP did not translate into shorter length of stay or improved complication rates.

## Conclusion

The role of “just-in-time” or perioperative PAP therapy intervention and effect on outcomes has yet to be determined. Emphasis has been placed on preoperative screening for suspect OSA and minimizing risk for known and suspect OSA patients perioperatively. Our institution has implemented in-hospital sleep consultative services in combination with OASIS with a close follow through protocol to aid workup and initial management of perioperative inpatients with suspected OSA. Many hospitals throughout the country have adopted their own approaches in screening and monitoring suspect and known OSA patients perioperatively. As long as perioperative outcomes in this population varies by institution, perioperative outcomes in OSA patients will likely be a future element for judging best practice performance.

In the absence of robust prospective outcomes data to guide us in the monitoring and postoperative management of OSA patients undergoing surgery, we must continue to develop best practices to avoid situations that we do not realize are dangerous [89] so that we do not end up involved with what has become known as the prototypical OSA postoperative malpractice case. But how do we know that the prototypical case involves severe OSA, morbid obesity, abdominal incision, narcotics, extubation without CPAP or supplemental oxygen, an unmonitored setting, and a relatively isolated ward room? Unexpected sudden death registries such as the ASA Closed Claims Project have helped. The project’s purpose is to identify major areas of loss in anesthesia, patterns of injury, and strategies for prevention. By combining preoperative screening, perioperative optimization, and identification of recurrent postoperative and PACU events, optimal risk identification, prevention, and intervention will hopefully be achieved as we pursue more robust prospective outcomes data.

## Summary of Keypoints

- Perioperative complications occur more commonly in those with OSA and can have significant impact on patient outcomes.
- Early identification of patients with OSA may forewarn the clinician of potential difficulty with airway maintenance intra- and postoperatively, perhaps influencing choice of anesthetic technique and postoperative monitoring environment.
- In the last several years, questionnaires have been developed with validation in the preoperative setting.
- When additional factors were included, the STOP-Bang Questionnaire had the highest sensitivity, especially for patients with moderate to severe OSA.
- Algorithms developed to minimize perioperative risk in those with known or suspected OSA take into account the patients’ risk of suspected OSA, severity of known OSA, type of surgery, comorbidities, and changes in OSA status.
- Perioperative OSA precautions may include anticipating possible difficult airway experiences, the use of short-acting anesthetic agents, opioid minimization, full

reversal of neuromuscular blockade verified prior to extubation, and extubation in a nonsupine position.

- A multimodal approach to minimize postoperative opioids may include peripheral nerve block catheters or neuro-axial catheters dispensing local anesthetic agents, nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, acetaminophen, pregabalin, tramadol, dexamethasone, ketamine, clonidine, gabapentin, or the nonopioid sedative dexmedetomidine.
- Taking into account 2006 ASA guideline and recent evidence for identifying patients most at risk for postoperative respiratory complications, we advocate an algorithm using recurrent PACU events as a predictive indicator to guide postoperative disposition of the known or suspected OSA patient.
- For those with previously undiagnosed but suspected OSA in the postoperative or medical inpatients setting, our institution has developed an OASIS protocol.
- Follow through is imperative for attempted initiation of empiric PAP, as indicated by poor overnight or PACU oxygenation, coronary artery disease, congestive heart failure, or arrhythmia, among others.
- While sustained high interest has driven preemptive or protocol-directed PAP therapy as we discuss in the context of general surgery, orthopedic surgery, and gastric bypass surgery patients, the role of “just in time” or perioperative PAP therapy intervention and effect on outcomes has yet to be determined.
- Perioperative OSA outcomes are a ripe target for best practice performance, as are missed prototypical OSA postoperative mortalities ripe targets for malpractice claims.

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# Chapter 20

## Sleep and Critical Illness

Nimesh Patel and Sairam Parthasarathy

**Keywords** Sleep • Critical illness • Mechanical ventilation • Artificial respiration  
• Noise • Intensive care unit

### Introduction

Sleep is vital for health and well being and involves a complex set of neuro-physiological processes [1]. A complex set of derangements characterize critical illness, and involve almost every organ system, including the neurological system. It follows that when these two spheres of complexity meet, i.e., the study of sleep during critical illness assumes an even higher level of complexity. Despite such hurdles, the potential rewards to better understanding sleep during critical illness have immense bearing to both sleep medicine and critical care fields [2]. While the field of sleep medicine needs further mechanistic data to determine the effect of sleep on survival, existing evidence suggests that sleep disturbances exert deleterious effects on patients with critical illness. Therefore, the focus of this chapter is to provide the reasons as to why, and what, a pulmonologist needs to know about sleep and critical illness.

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## Why Care?

Why should a pulmonary and critical care specialist care about sleep during critical illness? Emerging evidence supports the notion that severe sleep derangements during critical illness may influence the outcome and the perception of patients regarding their care. Specifically, inability to sleep due to high noise levels is among the top complaints of hospitalized patients [3]. When survivors of critical illness were asked to rate their sleep quality, subjects reported worse sleep quality in the intensive care unit (ICU) when compared to that at home [4]. The subjective nature of such reports do not detract from the study findings, in that, the reduction in perceived patient satisfaction is central to patient-centered care [3]. Therefore, reduction of noise levels is an important consideration in guiding design and construction of hospital facilities [3].

Sleep disturbances are associated with many objective adverse effects. For instance, a small prospective observational cohort of patients ( $n=24$ ) who suffered blunt head injury, sleep-wakefulness organizational patterns in the sub-acute stages of post-traumatic coma was associated with survival and functional recovery [5]. In this study, organized sleep patterns – i.e., sleep organized into well-recognizable non-rapid eye movement (NREM) and REM sleep that were alternating with each other – was associated with better outcome (OR 10.8;  $P=0.01$ ). In the same study, the 24 h polysomnography-derived sleep-wakefulness organizational state or lack thereof was more predictive of outcome than neuro-radiological findings, age, or Glasgow coma scale. However, these studies offer interesting preliminary observations that require validation in large, controlled longitudinal studies [5].

In another prospective observational cohort, the proportion of patients with abnormal sleep in patients who failed a trial of non-invasive ventilation was greater than in those who were successfully treated [6]. Moreover, in this study, patients failing non-invasive ventilation had worse sleep quality with greater circadian sleep-cycle disruption and less nocturnal REM sleep than those who were successfully treated with non-invasive ventilation [6]. Moreover, in a study of medically ill patients receiving mechanical ventilation, Watson and colleagues demonstrated that burst-suppression in EEG – derived from automated bispectral index (BIS) monitoring – was associated with greater mortality (hazard ratio, 2.04; 95% confidence interval, 1.12–3.70). However, polysomnography was not conducted in this study. Although such a body of data is accumulating with regards to the relationship between EEG-derived brain states and patient outcomes, as in all observational studies, whether such sleep-wakefulness or altered brain states play a causative role or are mere associates is less clear [2].

The effect of sleep deprivation on survival has been demonstrated in several animal studies. [7]. Specifically, in a cecal ligation and puncture model of sepsis, mice that were subjected to sleep deprivation were more likely to die than mice in the control group [7]. Moreover, in another sepsis model, administration of dexmedetomidine – a sedative known to promote true endogenous sleep – was associated with reduction in inflammation and mortality rate [8]. However, sleep or EEG-derived brain states were not measured in this study [8]. There is preliminary evidence that sleep

fragmentation may contribute to increased mortality in humans who are hospitalized for a critical illness [9]. However, more definitive intervention-based studies need to be performed in order to confirm a causal role of sleep disruption in mortality due to critical illness.

## Measurement of Sleep During Critical Illness

Several excellent reviews summarize the extent and effect of sleep disturbances on outcome in critically ill patients [10–13]. For example, sleep derangements are more pronounced in critically ill patients receiving mechanical ventilation, as compared to ambulatory patients; however, there is large variability in the nature and severity of sleep derangements reported [10]. For example, some investigators have reported that such patients spend 50% of the recording time in a 24 h period in slow wave sleep, whereas others have observed little (3–9%) or no slow wave sleep in critically ill patients [14–17]. Such large variability in the assessment of sleep in critically ill patients may, in part, be due to difficulty analyzing EEG, secondary to the confounding effects of sedative medications, underlying illnesses such as sepsis, and measurement artifacts in the ICU environment [18]. Therefore, automated methods, such a EEG spectral analysis, may be more reliable than manual methods using traditional scoring criteria in critically ill patients receiving mechanical ventilation [19]. However, automated methods do not capture pathological wakefulness states – wherein the patient is behaviorally awake but displays a sleep EEG pattern [6]. Video-assisted polysomnography may allow the distinction of such pathological wakefulness states; however, the reproducibility of assessing the behavioral states of critically ill patients is as yet unknown [2]. Nevertheless, there is a dire need for standardized and validated means of assessing the brain states of critically ill patients, and to link the findings to tangible patient outcomes.

Other methods of assessing sleep in the ICU include behavioral assessment, questionnaires, and Actigraphy [20, 21]. In a small observational study, actigraphy and behavioral assessment by the nurse were found to be inaccurate and unreliable methods to monitor sleep in critically ill patients [21]. Similarly, in an intervention-based study involving melatonin, Bourne et al. found that sleep efficiency inferred from BIS was not correlated with actigraphy or nurse assessment of sleep [22]. In this study by Bourne et al., a threshold BIS score of less than 80 was used to infer sleep; however, such a threshold was previously identified to indicate onset of sleep in healthy volunteers and was not validated in critically ill patients [23]. In contrast, other investigators found good correlation between quiet periods measured by actigraphy and sleep time estimated by nurses [24]. But, these investigators did not measure sleep using EEG [24]. A comprehensive review of various sleep measurement methods used to study sleep during critical illness were compared and the pros and cons of various methodologies – that included conventional polysomnography, BIS, actigraphy, nurse and patient self-assessment – were critically assessed [25]. Patient sleep self-tools that were reviewed included the Verran/Snyder-Halpern Sleep Scale, Hospital Anxiety and Depression Scale, sleep in the

ICU questionnaire, and Richards-Campbell sleep questionnaire [25]. This critical review concluded that polysomnography was still considered the gold-standard but suffered from feasibility concerns, whereas patient self-reports were limited by patient misperception and impaired cognitive state [25]. Nurse assessment of critically ill patients' sleep was both labor-intensive and unreliable.

In summary, research studies of sleep during critical illness in patients receiving mechanical ventilation should include EEG-based assessment of sleep with concomitant video recordings. Analysis of EEG may involve spectral analysis, sleep-wakefulness organizational state or R&K methodology (REM sleep features), and delineation of pathological or dissociative sleep states using simultaneous video recordings [6, 18]. Reliable clinical tools for measurement of sleep during mechanical ventilation in critically ill patients are currently not available. Whereas, in spontaneously breathing and cognitively intact patients residing in the ICU, subjective sleep assessment tools may be feasible but are prone to patient misperception.

## Nature and Extent of Sleep Disturbances

The ICU environment promotes sleep derangements. However, it is uncertain whether critically ill patients suffer from *sleep deprivation*. Some investigators have reported adequate sleep time (7–10 h/day) in critically ill patients [13, 14, 26]. However, others have reported reduced sleep times (3–6 h/day) [27]. Nevertheless, even in the studies that reported “adequate” average sleep times, there was wide variation in amount of total sleep time ranging from 2 to 19 h over a 24 h period [14]. Therefore, sleep deprivation is common in critically ill patients; however, other factors such as amount of sedatives, acuity of illness, and level of analgesia may be playing confounding roles.

*Sleep fragmentation* is another potential cause of sleep derangement in the ICU. [16]. Sleep fragmentation, measured as the sum of arousals and awakenings, show wide inter-patient variability. In some studies, sleep fragmentation as high as 63/h have been noted and in others sleep fragmentation was found to be much lower (13/h) [17, 26]. Such differences may be attributable to difference in sedation targets and practices. For example, in the study involving continuous sedation and paralysis, the sleep fragmentation measures were as expected much lower [17].

*Decreased REM sleep* is a consistent finding in critically ill patients [10]. Medications such as benzodiazepines, narcotic analgesics, critical illness, or mode of ventilation may be responsible for the paucity of REM sleep in this population [6, 13, 15, 17, 28]. Slow wave sleep was noted to be increased in some investigators, but this may have been due to the heavy sedation employed in such patients who were receiving non-depolarizing muscle paralytics [17]. Most other studies have demonstrated a paucity of slow wave sleep [10, 12].

Atypical patterns of sleep have been observed in critically ill patients who are receiving mechanical ventilation [13]. Cooper et al. categorized such patients as not having EEG characteristics of stage 2 (now N2) NREM sleep – such as K complexes

and spindles [13]. Some of these patients were noted to have brain states of pathologic wakefulness – characterized by behavioral correlates of wakefulness (saccadic eye movements and sustained electromyogram (EMG) activities) coinciding with EEG features of slow wave sleep which is not seen during wakefulness. Other groups have reported such states with video-recording based observations that are compatible with “abnormal” wakefulness, whilst the EEG is demonstrative of sleep [6]. Roche-Campo et al. went a step further by interacting with these patients to assess their responsiveness and assess the EEG-response to eye opening and closing.

Circadian rhythm is also abnormal in critically ill patients. The amplitude of circadian – measured as fluctuation in urinary metabolite of melatonin every 4 h – was markedly lower in septic critically ill patients when compared to non-septic critically ill patients or healthy controls [29]. Other investigators have studied circadian rhythms in critically ill patients by measuring serum and/or urinary melatonin levels that suggested that a majority of medically critically ill patients lacked circadian rhythms [30]. Critically ill patients with brain injury may have a greater depression of the amplitude of their circadian pattern as measured by serum melatonin and cortisol levels than medically ill patients in the ICU [31, 32]. Other methods of measuring circadian rhythm, such as sleep and temperature nadirs have revealed a lack of circadian rhythm in medical and post-operative critically ill patients [13, 33].

Causes and Cures

Numerous causes for sleep derangements during critical illness exist (Table 20.1). Environmental influences (such as noise, provider interactions, and light), medications, mechanical ventilation, pain, acuity of underlying illness and other factors including co-existing medical illnesses may all contribute to sleep derangements during critical illness. Each of the causes of sleep derangement will be discussed in the context of potential cures.

Table 20.1 Causes of sleep disruption in critically ill patients
Mechanical ventilation
Mode of ventilation
Level of ventilator assistance
Patient-ventilator dyssynchrony (Non-triggering and central apneas)
Environment
Noise
Light <sup>a</sup>
Temperature <sup>a</sup>
Patient care activities
Medications
Acuity of illness

<sup>a</sup>More evidence is needed.

The ICU is generally a noisy environment with noise levels ranging from 50–75 dB with peaks upwards of 90 dB [10]. Such noise levels far exceed the nighttime noise levels recommended by the WHO [34]. Nearly 21% of the sleep fragmentation episodes were attributable to spikes in noise level by Gabor et al. [27]. Application of mixed frequency white noise in a simulated ICU noise environment can reduce sleep fragmentation in healthy volunteers, but a similar study has not been performed in critically ill patients [35]. Other methods to reduce noise levels would be providing single rooms with sound insulation, education of care providers, and installing visual noise displays in the ICU room to alert or make care providers aware of the noisy environment in an effort to reduce noise levels [27, 36].

Visits by healthcare providers may be associated with noise or touch, i.e., care giving – in the form of physical therapy, bath, checking vital signs, repositioning, or treatment administration by nurse or respiratory therapist. Limiting or coordinating such care may reduce the number of interruptions but this has not been studied as a sleep-promoting intervention in critically ill patients. In hospitalized non-critically ill patients, a program designed to minimize nighttime awakenings of patients was associated with a reduction in nighttime sedative use [37]. In critically ill mechanically ventilated patients, Gabor et al. observed that such interaction with healthcare providers, as recorded on the video-polysomnography, accounted for 10% of the sleep fragmentation episodes. Other ICU environmental effects such as light and temperature may be influencing sleep in critically ill patients, but these have not been critically studied using intervention-based approaches. Conceivably, the derangements in circadian rhythm observed during critical illness may be attributable to the well-lit ICU environment – with light being the most powerful *zeitgeber* (“time giver” in German). However, this conclusion requires studying the effect of light-based intervention on sleep in the ICU environment.

A body of literature has been evolving in the study of the effect of mechanical ventilation on sleep during critical illness. A significant proportion (about 40%) of patients in the ICU requires mechanical ventilation, and studies have demonstrated significant sleep derangements in such patients as delineated earlier in this chapter. However, not all of the sleep derangements in such patients may be due to mechanical ventilation per se – because, attendant factors such as nasogastric tubes, restraints, sedative and analgesic medications, frequent suctioning, and mouth guards may be in part responsible for discomfort and consequent sleep disruption. A rigorous way of evaluating the effect of mechanical ventilation on sleep quality may be to randomly assign patients to different modes or level of mechanical ventilation and even perform cross-over studies in order to minimize the effects of the known inter-patient variability in sleep quality.

In a cross-over, randomized, controlled study, assist control ventilation was associated with reduction in sleep fragmentation when compared to pressure support mode [16]. The worsening of sleep fragmentation during pressure support was noted to be due to the appearance of central apneas – which when ameliorated by the administration of deadspace – was associated with improved sleep efficiency and reduction of sleep fragmentation [16]. Interestingly, patients with heart failure were more likely to develop such central apneas while receiving pressure support ventilation.

Considering that the magnitude of pressure assist administered during pressure support ventilation may have bearing on the appearance of central apneas and consequent sleep disturbance. Fanfulla et al. have compared pressure support that was titrated by measuring transdiaphragmatic pressure (physiological) vs. clinically determined (usual) pressure support [38]. Physiological level of pressure support was achieved by reducing measured transdiaphragmatic pressure by 40–80% of that during spontaneous unassisted breathing and usual (clinically determined) pressure support was that which reduced  $\text{PaCO}_2$  by at least 5%. The investigators found that physiologically titrated pressure support was associated with better sleep efficiency, greater proportion of time spent in REM sleep, and such improvements in sleep were correlated with levels of ventilator non-triggering [38]. In this study, 3 of 9 (33%) of the patients manifested central apneas (5–33 events/h) during usual pressure support and the magnitude of central apneas were inversely correlated with the amount of REM sleep [38]. Toublanc et al. compared low levels of pressure support vs. assist control ventilation in a randomized controlled study with cross-over design involving patients with acute on chronic respiratory failure [39]. In this study, both objective and subjective sleep quality were better during assist-control when compared to pressure support ventilation. However, the investigators did not find central apneas which may be explained by the low levels of pressure support (6 cm  $\text{H}_2\text{O}$ ) and in that the majority of patients suffered from obstructive lung disease – which is expected to dampen the loop gain and decrease the risk for central apneas [40]. Yet another study compared three modes of ventilation – assist-control, automatically adjusted pressure support, and clinically adjusted pressure support – and found no effect of mode of ventilation on sleep quality [41]. In this study, pressure support was adjusted clinically (i.e., to keep respiratory rate less than 35 breaths/min and tidal volume at 6–8 mL/kg predicted body weight) or through a closed-loop knowledge-based system that maintains pressure assist at a level that avoids hypo- and hyperventilation.

In sum, these studies underscore the need for optimal adjustment of pressure assist in pressure support, with a lack of such need during assist-control ventilation. The clinical implications of such findings are that the clinician needs to be knowledgeable of the pitfalls of the mode and level of ventilator assistance. While assist-control mode of ventilation is forgiving, pressure support mode requires careful and constant titration making it more labor- and knowledge-intensive to ensure adequate sleep during mechanical ventilation.

Medications may influence sleep during critical illness. Benzodiazepines, narcotic analgesics, and propofol are commonly used sedatives in critically ill patients. Benzodiazepines decrease the time needed to fall asleep, decrease awakenings, increase sleep duration, and increase sleep efficiency but, they also increase the number of spindles, increase cortical EEG frequency (at low doses), decrease EEG amplitude and frequency (at high doses), and suppress REM and slow wave sleep. Although, the clinical importance of these EEG alterations is not clear, an ideal hypnotic should preserve normal sleep pattern. Narcotic analgesics also suppress REM sleep, cause a dose-dependent slowing of EEG, and suppress slow wave sleep [28]. In sum, a medicated state may resemble sleep on the surface, but may not provide the physiological benefits associated with true sleep.

Discontinuation of medications may also influence sleep in critically ill patients. Specifically, discontinuation of opiates can cause rebound of REM sleep in post-operative patients and lead to a resurgence of nightmares or hypoventilation accompanied by hypoxia in the post-operative patient [28]. Administration of norepinephrine or epinephrine can reduce REM and slow wave sleep, whereas corticosteroids can cause nightmares and reduction in REM sleep [42].

Unlike conventional sedative agents, dexmedetomidine (a centrally acting  $\alpha_2$ -adrenergic agent) promotes sleep through central sleep neuronal pathways [43]. Such promotion of endogenous sleep may be preferable, but there are no published studies evaluating polysomnography during dexmedetomidine administration. Besides medications, multi-component approaches to improving sleep through reduction of sedative need and reduction of environmental stimuli have been achieved by Inouye et al. [44]. However, in this study sleep quality was not measured in an objective fashion. The measures taken to minimize sleep disturbances in the elderly patients included unit-wide noise-reduction strategies (e.g., quiet hallways, vibrating beepers, and silent pill crushers) and consolidation of care delivery interruptions (e.g., vital signs, procedures, and rescheduling of medications) [44]. However, adherence to such sleep promotion measures was difficult in comparison to other aspects of this multi-component approach (such as mobilization).

## Conclusion

In conclusion, sleep derangements are quite severe in critically ill patients. In critically ill patients, mechanical ventilation, medications, environmental noise, and care giving can impact sleep quality. Many tangible outcomes such as poor neurological outcome in head trauma, non-invasive ventilation failure, delirium may be determined or associated with sleep during critical illness. However, intervention-based trials are needed to ascertain the relationship between these factors and sleep as well as identify and implement effective means for improving sleep in such patients.

## Summary of Keypoints

- Sleep disturbances are severe during critical illness.
- Mechanical ventilation, noise, patient-care activities influence sleep.
- Delirium, non-invasive ventilation failure, poor neurological outcomes are associated with sleep disturbances during critical illness.
- Improving sleep in critically ill patients is patient-centered care and good medicine.



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